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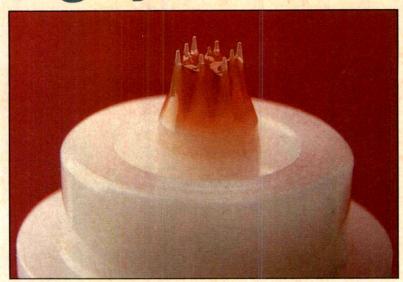
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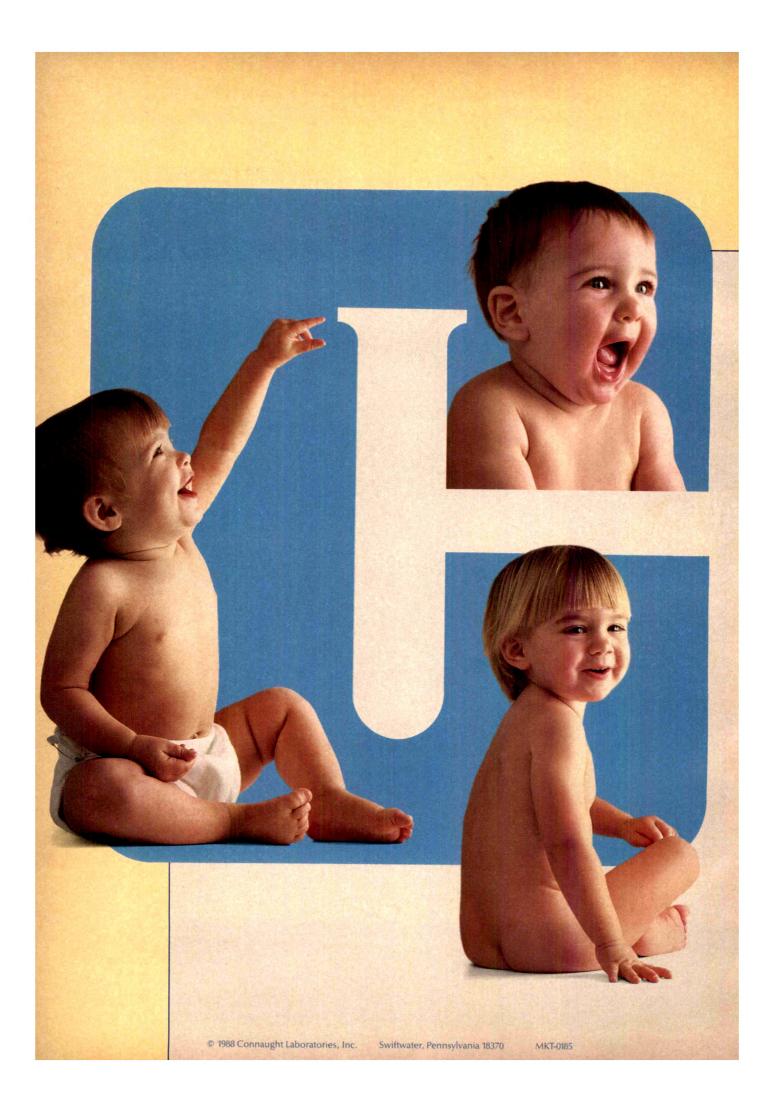
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Journal Articles: Sell EJ, Gaines JA, Gluckman C, et al: Persistent fetal circulation: Neurodevelopmental outcome. AJDC 1985;139:25-28.

Books: Krmpotic-Nemanic J, Kostovis I, Rudan P: Aging changes of the form and infrastructure of the external nose and its importance in rhinoplasty, in Conly J, Dickinson JT (eds): Plastic and Reconstructive Surgery of the Face and Neck. New York, Grune & Stratton, 1972, pp 84-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

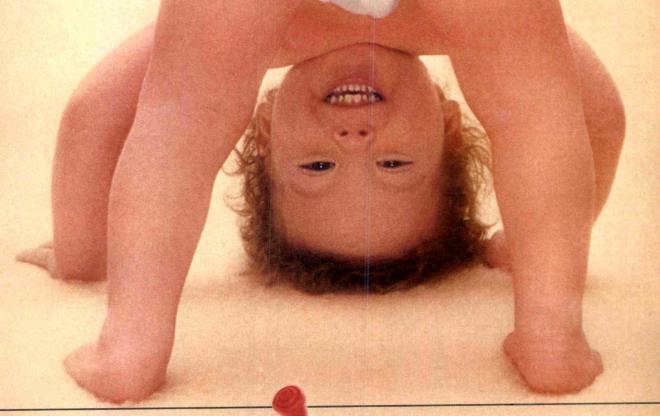
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- 5. Picture of the Month. Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.
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CONTRAINDICATIONS LOTRIMIN products are contraindicated in

WARNINGS LOTRIMIN products are not for ophthalmic use.

PRECAUTIONS General: If irritation or sensitivity develops with the use of clotrimazole, treatment should be discontinued and appropriate therapy instituted. Information For Patients:

The patient should be advised to:

1. Use the medication for the full treatment time even though the

1. Use the medication for the full treatment time even though the symptoms may have improved. Notify the physician if there is no improvement after four weeks of treatment.

2. Inform the physician if the area of application shows signs of increased irritation (redness, tiching, burning, blistering, swelling, oozing) indicative of possible sensitization.

3. Avoid the use of occlusive wrappings or dressings.

4. Avoid sources of infection or reinfection

Laboratory Tests: If there is lack of response to clotrimazole, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens before instituting another course of antimycotic therapy.

diagnosis and rule out other pathogens before instituting another course of antimycotic therapy.

Drug Interactions: Synergism or antagonism between clotrimazole and nystatin, or amphotericin B, or flucytosine against strains of C. albicans has not been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility: An 18-month oral dosing study with clotrimazole in rats has not revealed any carcinogenic effect.

In tests for mutagenesis, chromosomes of the spermatophores of Chinese hamsters which had been exposed to clotrimazole were examined for structural changes during the metaphase. Prior to testing, the hamsters had received five oral clotrimazole doses of 100 mg/kg body weight. The results of this study showed that clotrimazole had no mutagenic effect.

weight. The results of this study showed that clotrimazole had no mutagenic effect.

Usage in Pregnancy: Pregnancy Category B: The disposition of 14Cclotrimazole has been studied in humans and animals. Clotrimazole is very poorly absorbed following dermal application or intravaginal administration to humans. (See CLINICAL PHARMACOLOGY.)

In clinical trials, use of vaginally applied clotrimazole in pregnant women in their second and third trimesters has not been associated with ill effects. There are, however, no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. Studies in pregnant rats with intravaginal doses up to 100 mg/kg have revealed no evidence of harm to the fetus due to clotrimazole. High oral doses of lotrimazole in rats and mice ranging from 50 to 120 mg/kg resulted in embryotoxicity (possibly secondary to maternal toxicity), impairment of mating, decreased litter size and number of viable young and decreased pup survival to weaning. However, clotrimazole was not teratogenic in mice, rabbits and rats at oral doses up to 200, 180 and 100 mg/kg, respectively. Oral absorption in the rat amounts to approximately 90% of the administered dose.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly indicated during the first trimester of pregnancy.

numan response, this drug should be used only it clearly indicated during the first trimester of pregnancy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clotrimazole is used by a nursing woman.

Pediatric Use: Safety and effectiveness in children have been established for clotrimazole when used as indicated and in the recommended dear

ADVERSE REACTIONS The following adverse reactions have been reported in connection with the use of clotrimazole: erythema, stinging, blistering, peeling, edema, pruritus, urticaria, burning, and general irritation of the skin.

OVERDOSAGE Acute overdosage with topical application of clotrima-zole is unlikely and would not be expected to lead to a life-threatening

DOSAGE AND ADMINISTRATION Gently massage sufficient LOTRIMIN into the affected and surrounding skin areas twice a day, in the morning and evening.

Clinical improvement, with relief of pruritus, usually occurs within the first week of treatment with LOTRIMIN. If the patient shows no clinical improvement after four weeks of treatment with LOTRIMIN, the diagnosis should be reviewed.

HOW SUPPLIED LOTRIMIN Cream 1% is supplied in 15, 30, 45 and 90-g tubes (NDC 0085-0613-02, 05, 04, 03, respectively); boxes of

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LOTRIMIN Solution 1% is supplied in 10 ml and 30 ml plastic bottles (NDC 0085-0182-02, 04, respectively); boxes of one.

Store LOTRIMIN products between 2° and 30°C (36° and 86°F).

REFERENCE: 1. Among patients using LOTRIMIN Cream. Spiekermann PH, Young MD: Clinical evaluation of clotrimazole: A broad-spectrum antifungal agent. Arch Dermatol 112:350-352, March 1976.



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Delores Orfanakis, M.D. Emanuel Hospital & Health Center 2801 N. Gantenbein Avenue Portland, Oregon 97227 (503) 280-4637

References: 1. Oberfield SE, Levine LS: The child with short stature: NY State J Med; Essays in pediatrics; Jan 1986, 15-21.
2. Growth hormone in the treatment of children with short stature. Report of Ad Hoc Committee on Growth Hormone Usage, the Lawson Wilkins Pediatric Endocrine Society and Committee on Drugs AAP Pediatrics 1983; 72:891-94. 3. Glasbrenner K: Technology spurt resolves growth hormone problem, ends shortage, JAMA, 1996, 255 (5) 581-587. 4. Rosenfeld RG, Hintz RL: Diagnosis and management of growth disorders; Drug Therāpy, May 1983, 61-76.
5. Growth and growth hormone: Disorders of the anterior pliutiary, in Kaplan SA: Clinical Pediatric and Adolescent Endocrinology, WB Saunders Co. 1982. 6. Underwood LE. Rosenfeld RG, Hintz RL: Human Growth and Growth Disorders: An Update. University of North Carolina School of Medicine and Stanford University School of Medicine. October 1985.

Brief summary of prescribing information

PROTROPIN* (somatrem for injection)
INDICATIONS AND USAGE Protropin (somatrem for injection) is
indicated only for the long term treatment of children who have
growth failure due to a lack of adequate endogenous growth hormone secretion. Other etiologies of short stature should be

growth failure due to a lack of adequate endogenous growth hormone secretion. Other etiologies of short stature should be excluded.

CONTRAINDICATIONS Protropin (somatrem for injection) should not be used in subjects with closed epiphyses. Protropin growth hormone should not be used when there is evidence of any progression of underlying intracranial lesion. Intracranial lesions must be inactive and antitumor therapy complete prior to instituting therapy. Protropin growth hormone should be discontinued if there is evidence of recurrent tumor growth. Protropin growth hormone, when reconstituted with Bacteriostatic Water for Injection, USP (Benzyl Alcohol Preserved) should not be used in patients with a known sensitivity to benzyl alcohol as a preservative in Bacteriostatic Water for Injection has been associated with toxicity in newborns. When administering Protropin to newborns, reconstitute with Water for Injection. USP USE ONLY ONE DOSE PER VIAL AND DISCARD THE UNLESE PORTION.

PRECAUTIONS Protropin (somatrem for injection) should be used only by physicians experienced in the diagnosis and management of patients with pituitary growth hormone deficiency. Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process. Because Protropin growth hormone deficiency should have their glucocorticod replacement dose carefully adjusted to avoid an inhibitory effect or growth hormone. Protropin growth hormone were indicated. See WARNINGS to present with resistance with should have periodic thyroid function lesis and should be treated with thyroid hormone were indicated. See WARNINGS to use of Bacteriostatic Water for injection, USP (Benzyl Alcohol Preserved) in rewborns.

ADVERSE REACTIONS

with thyroid hormone when indicated. See WARNINGS for use of Bacterostatic Water for Injection, USP (Benzyl Alcohol Preserved) in newborns:

A Protropin (somatrem for Injection) Approximately 30 percent of all Protropin (somatrem for Injection) Approximately 30 percent of all Protropin treated patients developed persistent antibodies to growth hormone. In patients who had seen previously treated with pituliary demands and the protropin treated patients developed persistent antibodies to growth hormone in response to Protropin therapy in children not previously freated with pituliary demands and the protropin therapy in children not previously freated with any agogenous growth hormone approximately 40 percent developed persistent antibodies are not neutralizing and do not interfere with the growth response to Protropin growth hormone. In general, the growth hormone antibodies are not neutralizing and do not interfere with the growth response to Protropin growth hormone for 6 to 36 months developed antibodies associated with high binding capacities and failed to respond to treatment with Protropin growth hormone in addition to an evaluation of compliance with treatment program and flivriol status, testing for antibodies to human growth hormone should be carried out in a group of patients after approximately two years of treatment to detect other potential adverse effects of antibodies to growth hormone that the protropin growth hormone antibodies to growth hormone of the IgE class were detected. Testing included immune complex determined to be of the IgE class, no antibodies to growth hormone of the IgE class were detected. Testing included immune complex determined to make yet by with hormone antibody formation were observed. These lindings are supported by a toxicity study conducted in a primate model in which a similar antibody response to growth hormone was observed. Protropin growth hormone at the same doses and with placebover a period of 90 days. Most monkeys treated with high-dose Protropin growth hormone

was also examined for the presence of immune complexes and possible toxic effects of immune complexes by immunohistochemistry and electron microscopy.

B. Bacteriostatic Water for Injection, USP (Benzyl Alcohol Preserved) Toxicity in newborns has been associated with benzyl alcohol as a preservative (see WARNINGS).

OVERDOSAGE The recommended dosage of up to 0.1 mg (0.2 IU) per kg body weight three times per week should not be exceeded due to the potential risk of side effects.

DOSAGE AND ADMINISTRATION The Protropin (somatrem for injection) dosage must be individualized for each patient. A dosage and schedule of up to 0.1 mg/kg (0.2 IU/kg) body weight administered three times per week (1.1.w.) by inframuscular injection is recommended. After the dose has been determined, reconstitute each 5 mg vial with 1-5 mL of Bacteriostatic Water for injection, USP (Benzyl Alcohol Preserved) only. For use in newborns see WARNINGS. The pH of Protropin after reconstitution is approximately 7.8. To prepare the Protropin solution, inject the Bacteriostatic Water for injection, USP (Benzyl Alcohol Preserved) into the vial of Protropin growth hormone, aiming the stream of liquid against the glass wall. Then swift the product vial with a CENTLE Critary metion until contents have completely distinguish hormone be administered using sterile, disposable syringes and needles. After reconstitution, vial contents should be clear, without particulate matter it is solution is cloudy or contains particulate matter the contents MUST NOT be injected. Before and after injections the septim of the vial should be wiped with an antiseptic solution to prevent contamination of the contents after repealed needle insertions. The syringes should be clear repealed needl

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Some important clinical guidelines for patient identification

- Record height at all routine pediatric examinations.⁴
- Compare with cross-sectional data on a standard growth chart.⁴
- Careful, consistent technique for measuring children's height is critical.⁴
- Growth rates of less than 5 centimeters (2 inches) per year before age five, or less than 4.5 centimeters (1.8 inches) per year after age five, are cause for concern and may warrant further evaluation.⁵
- Progressive deviation from a normal growth curve may become apparent at any time during childhood.⁵
- Measurements made over four to six months, that show a decline in growth rate, may signal the need to refer the child for further evaluation.⁶

Early intervention: Time to grow

 Early diagnosis of children lacking adequate endogenous growth hormone is desirable because younger children typically demonstrate better responses to treatment and better long-term results than older children.⁶

For further information, please call toll free 1-800-821-8590 or 1-800-551-2231



X-ray child aged 8



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The Pediatric Forum

This department of AJDC is devoted to our readers. It is the place for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." In addition to the usual letters that comment on articles that have appeared in previous issues of AJDC, the Editor encourages our readers to express themselves on a variety of topics and issues that are considered to be important and that deal with current problems and other matters bearing on the health and welfare of children. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles. The latter contributions will be judged editorially, and may well be peer-reviewed in the usual fashion, or examined critically by our editorial staff in Tucson. Obviously, some may not be accepted for publication.

Acceptance of submitted letters will be contingent on both acceptability and space

available. The reader should submit double-spaced copy clearly marked "for publication" and signed by all authors. References, if included, should conform to the usual JOURNAL format. The maximum length of any contribution should be 500 words. Copyright assignment, signed by all authors, must accompany the original submission. The Editor reserves the right to edit all submissions. Although we will not impose a strict time limit on letters that apply to published articles in AJDC, in general these should be received within

six weeks of publication of the article.

Pediatricians and Careers in Health Care Management

Sir.—In the opening article of his excellent series on pediatric training, Michael Kappy, MD, PhD, addresses the changing role of the pediatrician. He indicates that many have left practice and opted for other careers, including administration.

A recent survey by the American Academy of Medical Directors confirms that pediatrics is one of the most common specialty backgrounds for physician executives.2 Some argue that pediatricians shift to administration as a way to improve income and relieve job burnout. An alternative explanation is that pediatricians are well suited by both disposition and experience for the unique demands of an administrative

Physicians who are used to seeing immediate results and working independently may be frustrated by the slowness of administrative remedies and by the constraints of working in bureaucratic organizations. In contrast, pediatricians are accustomed to the gradual pace of human growth and development, the ambiguities of pediatric diagnosis (many of our patients do not talk), and the advantages of a team approach to health care.

I believe that pediatric residents should be exposed to basic management concepts to assist them in preparing for office practice and to introduce them to the opportunity for a satisfying career in health care management.

> EDWARD H. LIPSON, MD, MS Physician Consulting Services National Medical Audit Inc Three Embarcadero Center San Francisco, CA 94111

- 1. Kappy MS: The pediatric residency program of the future: I. The changing face of today's private pediatric practice. AJDC 1987;141:945-
- 2. Kirschman DR, Grebenschikoff JR: Physician Executive Compensation Report: A 1986 Survey of Salary and Benefits. Tampa, Fla, American Academy of Medical Directors, 1987, chap 7.

Mumps Occurring in Previously Vaccinated Adolescents

Sir.—I previously reported four cases of mumps in adolescents whom I had previously vaccinated with mumps virus vaccine in early childhood. In that report, I raised the question of the possible need for booster doses of mumps vaccine in children approaching puberty.

Since the start of 1986, there has been a marked increase in cases of mumps in the Chicago area. From January 1986 through the middle of November 1986, there were 1750 cases of mumps reported to the Board of Health of Chicago (mostly by schools and hospital clinics). The actual number in the Chicago area far exceeds this reported number since most physicians in private practice do not report cases of mumps.

The age distribution of the reported cases were as follows: 0 to 5 years, 298 cases; 6 to 10 years, 595 cases; 11 to 15 years, 640 cases; 16 to 20 years, 83 cases; older than 20 years, 29 cases; age not given, 105 cases. In my practice during this period, I treated 20 adolescents with mumps, all of whom had received the vaccine at the appropriate time.

In 1986, the Chicago area had almost 40% of the 6807 cases of mumps in the United States reported to the Centers for Disease Control in Atlanta. Why the Chicago area is experiencing this marked increase in mumps is unclear. The State of Illinois did not have a mandatory requirement of mumps vaccination for entering school until this year. However, many children received mumps virus vaccine when given the measles-mumps-rubella vaccine at 15 months of age or older.

In the first three months of 1987, the age distribution of children with mumps continues to show a high incidence in the 10- to 20-year-old group, many of whom had been previously vaccinated in early childhood. In one school reporting 38 cases, 24 adolescents had received mumps virus vaccine.

The need for a booster dose of mumps vaccine (at least for adolescents living in the Chicago area) becomes apparent when they are exposed to the virus either in school or in a family setting.

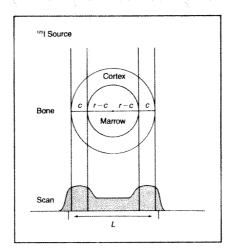
DANIEL J. PACHMAN, MD Professor of Pediatrics (Emeritus) University of Illinois and Rush Medical College 2315 E 93rd St Chicago, IL 60617

1. Pachman DJ: Mumps. AJDC 1979;133:332.

Decreased Bone Mineral Content = Rickets: A Misleading Equation

Sir-Rickets is a disease characterized by decreased mineralization of bone, a relative paucity of calcium and phosphate (apatite) in a matrix of cartilage.1 Therefore, one would anticipate a decrease not only in the total amount of minerals (ash) but also in the concentration or density of these minerals. If the volume of the matrix is constant (ie, no bone growth), then the estimates of total bone mineral and bone mineral content (BMC) per cubic centimeter are linearly correlated. If, however, bone size increases, as can happen in both normal and rachitic bone,1 then BMC could increase or remain constant, while bone density might remain constant or fall. Therefore, a distinction must be made between delayed bone growth (slowed matrix formation) and decreased bone density. Delayed bone growth may be one manifestation of widespread nutritional deficiencies, whereas rickets results from deficiencies of or failure to utilize calcium, phosphate, or vitamin D.1

The clinical estimate of bone mineralization is best accomplished in theory with photon absorptiometry. Technical difficulties make results from this technique variable.24 The technique measures the absorption of photons by bone from an iodine 125 source as it is moved along the radial axis of a long bone. Absorption is directly proportional to the amount of ash (mineral) in the path between the photon source and scintillator counter. The attenuation of the beam is proportional to the amount of mineral in the beam path, which in turn is proportional to the volume of bone scanned. Since the beam has a defined width, the beam's attenuation is proportional to the cross-sectional area of the bone scanned. The resultant counter output is the area of the absorption spectrum (the hatched area in the Figure). This number is then routinely divided by the length of the bone scan (equal to



Schematic representation of measurement of bone density by photon absorptiometry. Photons are emitted by an iodine 125 (125) source that moves across bone. Radiation is counted, and relative absorption is displayed. Density is determined by comparison to bone standard.

width of bone at scan site) to give the BMC expressed in milligrams per centimeter. This expression is *not* bone density and does not take into account the three-dimensionality of bone, which determines density.

The area under the absorption spectrum (AUC) is directly proportional to the cross-sectional area of the cortex, assuming a relatively homogeneous cortical density and low contribution of the marrow. Even if the marrow absorbs significant amounts of radiation, the relationships that follow are maintained, although the mathematics are slightly different. For simplicity, bone is considered a cylinder, but the only required assumption is that during growth, long bones grow in three dimensions: length, width, and thickness.

If D = density of bone = mineral content per cubic centimeter;

A = cross-sectional area, V = volume of sampled cortex;

L =length of absorption scan = width of bone;

r = radius of bone, c = cortical thickness, and a = c/r;

and assuming L=2r and t=thickness of beam and is constant,

then
$$A = \pi r^2 - \pi (r-c)^2$$

 $= \pi r^2 - \pi (r-ar)^2$
 $= \pi (r^2 - [r^2 - 2ar^2 + a^2r^2])$
 $= \pi r^2 (2a - a^2)$
and $V = At = \pi r^2 t(2a - a^2)$
 $V = \pi r^2 (t[2a - a^2])$.

Thus, $V = Kr^2$, where $K = \pi t(2a - a^2)$, which is constant if the ratio of c to r

is constant. Since the absorption is proportional to the total amount of minerals in the beam's path, the following equation gives the density of bone (ie, concentration of minerals):

$$D = \frac{\text{AUC}}{V} = \frac{\text{AUC}}{Kr^2} = \frac{\text{AUC}}{\frac{K}{4}L^2}$$
(equation 1)

Density is therefore proportional to AUC and inversely proportional to the square of the width of the bone.

It is clear that BMC expressed as milligrams per centimeter does not take into account the relatively cylindrical nature of long bones and the fact that bones get larger in all dimensions. The changes in cortical thickness may not be in exact proportion to r (ie, a may not be constant), but only if c were constant would A and, therefore, V and D, be linearly proportional to L:

$$A = \pi r^2 - \pi (r - c)^2$$

$$= \pi c (2r - c)$$

$$= \pi c (L - c)$$

$$= \pi c (L - c)$$

$$D = \frac{AUC}{K(L - c)}$$

This is not likely. It is more likely that c increases as L increases. Data on metacarpal bones from childhood show this to be the case.⁵

The AUC must be divided by L^2 to get an estimate of density (the third dimension, thickness, is incorporated into the AUC) (equation 1). This relationship is described by Greer and McCormick. Unlike BMC and post-conceptual age, which are exponentially related, BMC/L at birth is linearly related to gestational age, and the slope is shallow: from 10 mg/cm² at 28 to 29 weeks to 16 mg/cm² ten weeks later. The BMC rises from 35 mg/cm to 90 mg/cm in ten weeks.

Numerous groups^{3,4,6,7} have studied bone density by photon absorption. With one exception,⁴ the authors examine BMC (as milligrams per centimeter), not bone density. I suggest that while this value is important as one of several measures of growth, it is not a marker of rickets. Bone density should be calculated when testing any hypothesis regarding rickets.

KENNETH HARKAVY, MD Department of Neonatology Columbia Hospital for Women 2425 L St NW Washington, DC 20037

1. Aurbach GD, Marx SJ, Spiegel AM: Parathyroid hormone, calcitonin, and the calciferols, in Williams RH (ed): *Textbook of Endocrinology*, ed 6. Philadelphia, WB Saunders Co, 1981, pp 1000-1006.

2. Tyson JE, Maravilla A, Lasky RE, et al: Measurement of bone mineral content of preterm neonates: Reliability of the Norland densitometer. AJDC 1983;137:735-737.

3. Minton SD, Steichen JJ, Tsang RC: Decreased bone mineral content in small-for-gestational-age infants compared with appropriate-for-gestational-age infants: Normal serum

25-hydroxyvitamin D and decreasing parathyroid hormone. *Pediatrics* 1983:71:383.

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In Reply.—We fully agree with Dr Harkavy's observation that low BMC is not equivalent to rickets. The common confusion of these two appears to arise from misunderstanding about what quantity is represented in BMC. Although Dr Harkavy points out one aspect of this misunderstanding, his letter suffers from several others.

The letter states that BMC is not bone density. There are, of course, nearly as many types of density as there are denominators. Of particular relevance to the measurement of BMC are linear density, area density, and volume density. Linear density relates most closely to bone quantity and is expressed in mass per unit length. Bone mineral content is an example of a linear density. Area density is the quantity that determines roentgenographic absorption and is expressed in mass per unit area. Volume density relates most closely to bone quality (ie. rickets) and is expressed in mass per unit volume. It has been our experience that the most common cause of confusion and disagreement about the applicability of bone absorptiometry arises from confusion of these three types of density. Contrary to Dr Harkavy's claims, the BMC is derived directly from the integral of the absorption curve. Division by the bone width (BW) yields a separate index that has no established name and is simply referred to as BMC/BW. This index is, of course, an area density and is expressed in grams per square cen-

Dr Harkavy's fundamental observation is fully valid. Many of the early workers in the field of bone absorptiometry struggled to develop ways to

determine volume density from a linear image. Their efforts met with disappointment, largely because of a practical inability to establish an index of volume density that was more clinically effective in identifying bone pathologic characteristics than linear or area density. It appears that the root of this difficulty lies in the breakdown of an assumption required by Dr Harkavy's equation 1: that cross-sectional area is proportional to the square of BW. Diaphyses are not only highly noncylindrical, but the shape of their cross sections varies widely. As a result, BW varies from one individual to another with the same crosssectional area as well as in the same bone with rotation. As the BMC is divided by higher powers of BW, the variability of the relationship of BW to cross-sectional area affects the quotient more severely.

One is left with a question of practicality. Clearly, a linear density such as BMC is not a valid surrogate for a volume density. Until a method of estimating cross-sectional area is found that can be demonstrated to be more effective in identifying qualitative abnormalities of bone, we maintain the usefulness of combining BMC with other indicators of skeletal status in the evaluation of skeletal development

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Arterial Access and Monitoring in the Newborn

Sir.—In the August 1987 issue of AJDC, Randel and colleagues,¹ relating their experience with percutaneous peripheral arterial catheterization, mention common complications associated with umbilical catheterization; Goetzman² states that, until additional information becomes available, some caution must be used in selecting the site for peripheral arterial access in the newborn.

This controversy gives us an opportunity to remind neonatologists of another option too often neglected³: in our opinion, whenever possible, a noninvasive technique should be preferred. For example, in nearly all cases where only blood gases are to be moni-

tored, an arterial access is not mandatory. As for blood pressure monitoring, a slight reduction of accuracy with the noninvasive technique may be allowed without altering the quality of treatment because such a technique is without side effects.

Between January and December 1985, 210 infants admitted to the New York Columbia Presbyterian neonatal intensive care unit were considered to require an arterial line. During the same period in Strasbourg's neonatal intensive care unit, only 16 of 554 infants admitted were cared for with the more invasive approach; all others who needed this kind of monitoring were cared for with the alternative noninvasive approach.

It is always difficult to compare statistics from different neonatal intensive care units, but it is useful to bear in mind that a less aggressive method may often be preferable to arterial

catheterization.

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- 4. Rooth G, Huch A, Huch R: Transcutaneous oxygen monitors are reliable indicators of arterial oxygen tension (if correctly used). *Pediatrics* 1987;79:283-286.

Effects of Strength Training on Serum Lipid Levels in Prepubertal Boys

Sir.—In their study of serum cholesterol levels in prepubertal boys before and after a strength-training program, Weltman et all concluded that "a concentric strength-training program in prepubertal boys results in a reduction in serum cholesterol levels while maintaining the HDL-C [high-density lipoprotein cholesterol] level." This interesting study appears to have several methodologic problems that make such a conclusion difficult to justify.

Nineteen subjects were enrolled in a strength-training program while ten others were assigned to a control group. Nowhere is the reader told whether group assignment was randomized or whether such characteristics as body mass index, age, diet, and extracurricular habits of the two groups were similar. Prior to any intervention, the group assigned to the exercise program had a mean (±SD) serum cholesterol level substantially higher than that of the $control \quad group \quad (5.09 \pm 1.01 \quad mmol/L$ $[197.2 \pm 39.3]$ mg/dL] $4.14 \pm$ VS $0.56 \text{ mmol/L} [159.9 \pm 21.5 \text{ mg/dL}], \text{ re-}$ spectively). Although no tests of statistical significance were provided, it appears that the two groups were dissimilar at the beginning of the study.

In their discussion, the authors recognized the difficulty in lowering serum cholesterol levels in children whose initial levels were below 4.14 mmol/L (160 mg/dL),2,3 and yet they used such a group as their control. The authors also acknowledged previous studies that had described favorable reductions of elevated serum cholesterol levels by such means as exercise or diet. Associating the exercise program with reduced serum cholesterol levels would be justified only if the changes in cholesterol levels could be shown to be independent of the initial group differences.

In addition, the exercise program in this study had an aerobic-exercise effect. The improvement in maximal oxygen consumption in the exercise group suggests this argument. It would have been helpful to have reported a measure of the intensity of the exercise (eg, heart rates during the 30 minutes of exercise) before attributing the benefits of the program to strength training or characterizing the program as a strength-training program.

It is unfortunate that these methodologic problems weakened the conclusions of this study because the study addressed several interesting and important questions.

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1. Weltman A, Janney C, Rians CB, et al: The effects of hydraulic-resistance strength training on serum lipid levels in prepubertal boys. AJDC 1987-141-777,780

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In Reply.—In response to Dr Mac-Mahon's letter, I would like to address the following points:

1. Subjects were randomly assigned to treatment groups. All subjects were recruited from the same sports teams, and all were interested in strength training. The experimental group underwent strength training, while control subjects were told that they would begin strength training at the end of the 14-week experimental period. (They did train after the strength training study was over.) This is mentioned in the "Pubertal Status" section of the article.

2. I am sensitive to the concern relative to initial group inequity. The possibility that the groups might differ prior to experimental treatment motivated the inclusion of a pretest in the

experimental design.

Although my colleagues and I considered the use of an analysis of covariance (ANCOVA) in this case, we preferred to use its repeated-measures analysis of variance (ANOVA) counterpart. The conflicts regarding which of the two methods to use, or possibly even some other techniques, is not a new matter. However, regression effects would likely not be corrected" any better with the use of ANCOVA than with its repeatedmeasures ANOVA counterpart. Incidentally, an ANCOVA was performed along with the repeated-measures ANOVA-with the same "bottom line"-and the experimental group showed a significantly more positive physiologic response than did the control group.

3. With respect to the comment that changes in serum cholesterol levels may be due to initial level differences (suggesting a regression toward the mean). I disagree with the suggestion that the change seen in total serum cholesterol concentration was not due to a treatment effect but rather to regression toward the mean. As stated previously, my group believes that an ANOVA with repeated measures is an appropriate statistical technique to determine a treatment effect. Furthermore, in support of a true treatment effect, the four experimental subjects whose serum cholesterol levels were 4.14 mmol/L (160 mg/dL) or lower on the pretest were examined for posttraining serum cholesterol levels. The pretest mean cholesterol value for these four subjects was 3.97 mmol/L (153.5 mg/dL), while their posttraining value was 3.57 mmol/L (138 mg/dL) (a

reduction of 0.40 mmol/L [15.5 mg/dL] in total serum cholesterol concentration). These data suggest that the treatment effect was uniform across individuals of varying initial serum cholesterol levels, thus supporting a treatment effect rather than a regression toward the mean.

4. We agree with the concern regarding the aerobic-training effect. Subjects in the present study improved in maximal oxygen consumption; therefore, the changes in total serum cholesterol concentration may also ascribe to an increase in physical fitness in addition to strength training. We address this point toward the end of the "Comment" section. The physiologic responses to strength training have been described in detail previously.¹

I hope these comments have addressed the concerns raised by Dr MacMahon. I agree that our study addressed several interesting and important questions and hope that the findings will stimulate future investigation in this area.

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1. Weltman A, Janney C, Rians CB, et al: The effects of hydraulic-resistance strength-training in prepubertal males. *Med Sci Sports Exerc* 1986;18:629-638.

Detection of Pulsus Paradoxus by Pulse Oximetry

Sir. — In addition to measuring oxygen saturation noninvasively, the Nellcor N-100 pulse oximeter (Nellcor Inc., Hayward, Calif) also gives a qualitative display of the pulse amplitude of the vascular bed underlying the probe. This is displayed on the front of the monitor as a vertical 16-segment lightemitting diode (LED) post. This feature of the pulse oximeter may be useful in detecting and monitoring pulsus paradoxus, an exaggeration of the normal reduction in pulse pressure on inspiration, which is an important index of small airway obstruction during an acute asthmatic attack.

Patient Report.—While using the Nellcor N-100 pulse oximeter in a 12-year-old boy in severe status asthmaticus, alternating decreases and increases in the LED

pulse post of the pulse oximeter were observed in association with inspiration and expiration, respectively. The LED postexcursion decreased to one to two segments on inspiration but rose to ten segments on expiration. The pulse recorded on the pulse oximeter was identical to the true heart rate recorded simultaneously on a cardiac monitor, and the changes persisted despite oxygen saturations of greater than 95%. The boy's hand, on which the probe was applied, was perfectly still, and the changes in the LED post were thus not related to motion artifact. A pulsus paradoxus of 40 mm Hg was measured simultaneously by sphygmomanometry. As the boy's clinical condition improved with inhalations of albuterol (Ventolin inhaler) and ipratropium bromide, the LED post equalized on both inspiration and expiration, and a pulsus paradoxus was no longer detected by sphygmomanometry. A further exacerbation associated with a pulsus paradoxus occurred on the following day, and similar changes were observed on the LED pulse

Comment.—The Nellcor N-100 probe consists of an LED that emits light at two constant wavelengths (660 and 990 nm) and a photodetector placed on either side of a pulsating vascular bed. The instrument functions as a plethysmograph, in that it measures the volume changes of the underlying vascular bed as it expands and contracts. The apparent lighted height of the pulse post rises with increases in pulse volume amplitude (PVA) and vice versa.

The exact derivation of the PVA is complex and depends on a number of factors apart from the size of the arterial pulse wave, including the oxygen saturation of the arterial blood, the wavelengths of light used, 'cutaneous blood flow,' and motion artifact.' Kim et al' have suggested that the PVA is primarily influenced by blood volume changes in veins and venules, generated by shunting through cutaneous arteriovenous anastomoses rather than by directly transmitted arterial and arteriolar pulsations per se.4

Nevertheless, the variations in the LED pulse post appeared to be related to pulsus paradoxus in this case. The pulse post may therefore add to the value of the pulse oximetry in monitoring the response to therapy in acute asthma. It is not a calibrated instrument, however, and remains a qualitative, not a quantitative, indication of

perfusion.

C. Anthony Ryan, MB, MRCPI IWK Hospital for Children Intensive Care Unit PO Box 3070 Halifax, Nova Scotia B3J 3G9 Canada 1. Yelderman M, Corenmen J: Real time oximetry, in Prakash O (ed): Computing in Anesthesia and Intensive Care. The Hague, Martinus Nijhoff Publishers, 1983, pp 328-341.

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Comment on the Assessment of Bone Mineral Status in Children

Sir—In a recent issue of AJDC, Specker and colleagues1 reported normal values for peripheral compact bone mineral content, as assessed by single photon absorptiometry in 89 preschoolage children. While we believe such research is of vital importance to the study of childhood growth and development, we must warn the unwary of potential discrepancies in the reporting of these results. While this article presents normal values for children aged 1 through 6 years, previous publications²⁻⁴ report bone mineral content as determined by the same technique for children aged 6 through 14 years, providing an overlap period at age 6 years so that data can be compared. The bone mineral content value for this age is given as $0.356 \pm$ 0.06 g/cm, whereas the extrapolated value found by Mazess and Cameron⁸ was 0.486 g/cm for boys and 0.475 g/cm for girls (a striking difference of 2 SDs). Certainly, geographic differences could account for some of the discrepancy, and, indeed, one publication suggests such interstate differences,5 although not of this magnitude. Moreover, normal values generated 15 years apart could be subject to cohort differences, machine upgrades, and modifications of scanning protocols, although one of us recently validated the original data using a normal adolescent female population and found consistent results in that age range using the same device as in the original publication (R.W.C., unpublished data, 1985). We are, consequently, at somewhat of a loss in explaining these disparate values, which were generated on similar instruments in healthy normal children at the same anatomic site. Caution, therefore, should be taken in the indiscriminate use of age norms for bone mineral content generated at different centers, even if the technology employed is assumed to be equivalent. Indeed, it may be appropriate to measure local standards in children in any given center.

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1. Specker BL, Brazerol W, Tsang RC, et al: Bone mineral content in children 1 to 6 years of age. AJDC 1987;141:343-344.

2. Mazess RB, Cameron JR: Skeletal growth in school children: Maturation and bone mass. Am J Phys Anthropol 1971;35:399-407.

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4. Chesney RW, Mazess RB, Rose PG, et al: Bone mineral status measured by direct photon absorptiometry in childhood renal disease. *Pediatrics* 1977;60:864-872.

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In Reply.—We appreciate Drs Block and Chesney's comments and would like to note that the values given in their letter (0.486 and 0.475 g/cm for boys and girls, respectively) at age 6 years are not the values that appear in the reference they give.1 However, though less striking, the correct values of 0.466 and 0.436, respectively, in the reference noted are still significantly different from our value of 0.356 g/cm. The difference is within 2 SDs of our mean. The difference in bone mineral content between the two populations is of concern to us, as well, and may indeed represent differences in ethnicity, diet, exercise, and other unknown factors. Until more information becomes available, it would appear prudent to use region-specific, in addition to race-, age-, and sex-specific, norms to evaluate bone mineral content in children.

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1. Mazess RB, Cameron JR: Growth of bone in schoolchildren: Comparison of radiographic morphometry and photon absorptiometry. *Growth* 1972;60:77-92.

Cytarabine Anaphylaxis

Sir.—The report by Berkowitz et al1 of anaphylaxis due to cytarabine in a child with acute promyelocytic leukemia is misleading in several respects. The patient is described as having "generalized anaphylaxis," although her bradycardia, profuse sweating, and pallor make this diagnosis unlikely. Anaphylaxis generally presents with tachycardia and flushing,24 unless other conditions, such as a myocardial infarction, supervene. The described hypotensive episode might represent hypoglycemia or hypercalcemia-both are possible in this setting and both would be expected to respond to hydration and intravenous epinephrine.

Furthermore, five controls, only two of whom had been exposed to cytarabine, tested negative. No statistical evaluation of these data is offered in the text. At best, the P value for this assay is .17 by Fisher's exact test. Since only children previously exposed to cytarabine would be expected to have antibodies to it, a more rigorous evaluation would yield a P value of .33.

It may be that this child had an elevated anti-cytarabine IgE level. However, without a convincing clinical correlation, an elevated urine histamine level, or at least a more physiologically meaningful positive in vitro test, such as basophil histamine release, I cannot agree with the authors' conclusion that this IgE is the cause of this child's catastrophic event.

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3. Kaliner M, Shelhammer JH, Otteson EA: Effects of infused histamine: Correlation of plasma histamine levels and symptoms. J Allergy Clin Immunol 1982;69:283-289.

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 Lichtenstein LM, Osler AG: Studies on the mechanisms of hypersensitivity phenomena: IX. Histamine release from human leukocytes by ragweed pollen antigen. J Exp Med 1964;120: 507-530. In Reply.—Dr Slater indicates that the symptoms and signs of the patient we recently described may not have been caused by generalized anaphylaxis but rather by hypoglycemia or hypocalcemia. The most likely alternative diagnosis, we believe, would have been a vasovagal attack^{1,2}; however, none of these conditions would have resulted in swelling of the lips.

We performed the in vitro studies to demonstrate the presence of circulating anti-cytarabine IgE in an attempt to provide other evidence, albeit circumstantial, that the reaction was indeed anaphylaxis. As Dr Slater points out, the results do not stand up to statistical analysis, which was clearly not attempted. Several methods have been used to provide nonclinical evidence of immediate hypersensitivity reactions, including the demonstration of circulating specific IgE antibodies.3 The method we used, namely, demonstration of anti-cytarabine IgE antibodies in the patient's serum by an enzyme-linked immunosorbent assay, was one readily available to us.

We cannot claim that we have provided irrefutable proof that our patient's collapse was the result of anaphylaxis due to cytarabine, proof that only a repeated challenge might provide and that we did not consider justified. Nevertheless, we believe we have provided sufficient evidence to make our diagnosis likely and our observation noteworthy.

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Use of Narcotics in Sickle Cell Disease

Sir.—Dr Mallouh, in responding to Dr Buchanan's discussion on the use of intravenous narcotics in sickle cell disease, raises an interesting consideration.

I agree that any physician treating a patient with a painful occlusive crisis of sickle cell disease must provide effective analgesia regardless of the means needed to do so. I also agree that through the proper use of morphine, in the presence of significant pain induced through nociceptive stimuli, the pain can be quite easily managed with the use of morphine sulfate by the oral route. I agree that carefully administered analgesia is essential and should not lead to drug addiction if properly used in a clinical titration manner, as used in terminally ill patients at my institution.

I only argue that this treatment can be done quite effectively by mouth using sublingual morphine or morphine solutions titrated carefully until the pain is controlled without affecting respiratory activity or modifying the level of consciousness. I argue for the oral route rather than any other route since it has been found to be quite effective in many patients of all ages with nociceptive pain. One should also recall that if the case is complicated by bone-induced pain, use of the nonsteroidal anti-inflammatory agents appears to be quite specific for the relief of such induced pain. At times a combination of drugs may be necessary depending on the cause and extent of the pain and associated symptoms.

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1. Mallouh AA: Intravenous narcotics in sickle cell crises. AJDC 1987;141:1039-1040.

In Reply.—I also believe that effective analgesia should be provided for patients with painful occlusive crises of sickle cell disease. Dr Holman states that nonsteroidal anti-inflammatory agents appear to be quite specific for

bone-induced pain and that a combination of drugs may be necessary. Nevertheless, he recommends oral morphine therapy for "significant"

Dr Holman also minimizes the possibility of drug addiction. Buchanan, in his reply to my previous letter, stated that "no data have been published in the literature showing that intermittent and carefully supervised high-dose narcotic therapy for severe painful crisis predisposes to drug dependency or addiction." However, he does not mention that there are no studies to the contrary.

My problem is the definition of severe as used by Dr Buchanan and significant as used by Dr Holman. Several patients have been seen in my clinic with what seemed to be severe pain, yet a dose of placebo (distilled water) gave them great relief. I believe that the important point is careful medical supervision. A close trust between the physician and his or her patients may decrease the need for narcotic therapy. However, I think that this mode of therapy should not be encouraged by physicians who occasionally treat patients with sickle cell disease and who do not closely follow up these patients.

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1. Buchanan GR: Intravenous narcotics in sickle cell crises. AJDC 1987;141:1040.

Chronic Lung Disease in Children **Born With Sublethal Lung** Hypoplasia

Sir.—Bell et al' have to be commended for focusing their attention on the long-term pulmonary outcome of two patients born with sublethal forms of lung hypoplasia. There is remarkably little information available in the literature on what happens to lung structure and function of these infants and children as they develop. Clinicians all too often assume that lung structure has normalized when the patient is asymptomatic and has a clear chest roentgenogram and normal pulmonary function study results. A very instructive case was reported in detail by Thurlbeck et al.² Their patient was born with a left-sided diaphragmatic hernia and hypoplastic lung documented at the time of the successful surgical repair. His chest roentgenogram and pulmonary function study

results were normal at 1 year of age and he died in an accident at age 5 years. At necropsy, the volumes of both lungs were normal, but the left lung contained four times fewer alveoli, which were larger, with grossly diminished alveolar surface area.

Bell et al theorize that the lung disease documented in their two patients was primarily lung hypoplasia resulting from oligohydramnios-induced compression from abdominal pregnancy. There is little doubt in my mind that the lack of amniotic fluid played the crucial role in impairing normal lung growth, as I verified this phenomenon in an animal model of uteroabdominal pregnancy.3 Whether fetal compression played an additional role is indeed a matter of conjecture at this point. It has been known for a while that the outcome of abdominal pregnancies depends a great deal on the integrity of the amniotic sac and the presence of amniotic fluid. Willard Allen, MD, "hit the jackpot" over 25 years ago when he delivered a set of twins from an abdominal pregnancy. One fetus was surrounded by intact membranes and amniotic fluid, while the other was only partially surrounded by membranes with no fluid. The first infant did well, whereas the second, with ruptured membranes. "never established normal respiration" and died within 12 hours.

Although the course of the lung disease described by Bell et al does not quite fit with the diagnosis of bronchopulmonary dysplasia, they were struck by the similarity of the roentgenographic findings in both conditions. They have described in a previous article similar findings in patients following premature and prolonged rupture of the membranes (with presumably some degree of lung hypoplasia at birth). In the multicenter study on the incidence of bronchopulmonary dysplasia,6 time and duration of membrane rupture was not documented. I wonder whether some of the difference in incidence between the centers studied might not be related in part to different obstetric approaches in the management of the fetus with premature rupture of the membranes.

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Chronic Lung Disease in **VLBW** Infants

Sir.—Kraybill et all presented a nearly complete data set about very-lowbirth-weight (VLBW) (501 to 1500 g) infants born in North Carolina in 1984, including the incidence of chronic lung disease (CLD). We have been accumulating similar data about all VLBW infants in our North Central Perinatal Region (NCPR) in Illinois for the period from 1985 through 1986. This data set includes information about 219 NCPR infants cared for in our center. 61 infants cared for in surrounding centers, and 19 infants who never received center care.2 We present herein a brief comparison between the North Carolina and NCPR experiences (Table). We also offer some comments pertinent to our common topic. A more complete report of our experience is in preparation.

The 19 NCPR infants not transferred to centers—infants who would have been missed by the system of Kraybill et al—are a mixed group. Only nine infants "were extremely immature infants who were considered not viable" and hence were not resuscitated (mean [±SD] birth weight, 616 ± 76 g). Four larger infants $(1053 \pm 163 \text{ g})$ were vigorously, but unsuccessfully, resuscitated. Two others had lethal congenital malformations. Four infants were relatively large (1206 ± 181 g) and survived without transfer to a center. Two of these latter four infants were the smaller members of twin sets.

We have struggled with the choice of proper denominators, including the one(s) to express the true incidence of CLD. The extreme variations in CLD frequency cited by Kraybill et al are, in large part, due to the choice of inconsistent and often incorrect denomina-

| Comparison of Regional Data on |
|--------------------------------|
| Chronic Lung Disease in VLBW |
| Infants* |

| | No. (%) of VLBW Infants | | | |
|------------------------------------|------------------------------|-------------------------|--|--|
| | North Carolina (1984)† | NCPR (1985- 1986) | | |
| Total births | 1147 | 299 | | |
| No "center" care | 52 (4.5) | 19 (6.3) | | |
| In data set | 1095 | 299 | | |
| In-hospital survivors | 805 (74) | 207 (69) | | |
| "At-risk" group | 446 | 108 | | |
| Chronic lung disease | 241 (54) | 50 (46) | | |
| Chronic lung disease at 3 mo | | | | |
| of age | 67 (15) | 17 (16) | | |

*VLBW indicates very-low-birth-weight (501 to 1500 g); NCPR, North Central Perinatal Region (Illinois) study.

†North Carolina study by Kraybill et al.1

tors. While their concept of the "atrisk" group has some appeal, it adds yet another denominator to an already-confusing scene. Another problem with the at-risk cohort, as defined, is that infants with prolonged respiratory insufficiency,4 who die before 30 days of age, are totally eliminated from consideration because they do not "meet criteria," even though they had very severe lung disease. Avery et al5 avoided the denominator dilemma by expressing data in terms of survival free from lung disease. Perhaps we have not yet found the proper denominator for expressing the incidence of CLD, or, more likely, there may be several proper denominators as dictated by the intended use of the data. Fortunately, Kraybill and coworkers stated the number of VLBW infants in their geographic area, which is the appropriate denominator for interregional comparisons.

Kraybill et al used the incidence of CLD for interunit comparisons and explored the relationships of CLD to unit size, status of university affiliation, presence or absence of house staff, and other factors. For such interunit comparisons to be more precise, adjustments should be made not only for birth weight but also for the race and gender mix of the VLBW cohort. Another important variable is

the inborn-outborn mix that Kraybill and colleagues totally ignored.

We, too, see a large number of CLD cases resolve favorably between 30 days and 3 months of age. Thirty of the 33 infants who left the CLD cohort during this time frame survived. Emphasizing this high rate of short-term resolution gives a more balanced view of CLD in the at-risk group.

Our congratulations to Kraybill et al. We are delighted to see others examine the VLBW cohort and its problems regionally rather than confining analyses solely to that segment of the cohort receiving care in one center.

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In Reply.—We are pleased that our report "played in Peoria." We thank Dr Powers and Ms Hegwood for their remarks and comparative data. The inhospital survival rate and incidence of CLD among VLBW infants in the NCPR of Illinois appear similar to those of North Carolina.

The choice of a proper denominator for computing the incidence of CLD is indeed difficult. Our denominator (all VLBW 30-day survivors who had received mechanical ventilatory support for >48 hours) includes the infants we believe to be at risk. Thirty-day survival is a necessary criterion for at-risk status if, by definition, CLD does not exist before age 30 days. Our other criterion, mechanical ventilatory support for longer than 48 hours, is somewhat arbitrary. For that reason we also presented our data using two other denominators: all VLBW 30-day survivors and all VLBW admissions.

Powers and Hegwood are correct in

pointing out that race, gender, and inborn-outborn ratios may have differed among the neonatal intensive care units we compared, and such differences may have contributed to the differing CLD rates we observed. We are now analyzing in detail a subset of the 1984 North Carolina VLBW cohort to determine the effect of those variables, as well as early treatment variables, on risk for CLD.

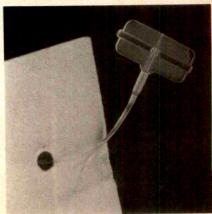
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Foreign-Body Aspiration

Sir.—Foreign bodies in the upper aerodigestive tracts of children are a common problem frequently marked by stridor, wheezing, and respiratory distress. The specialties of pediatrics and otolaryngology have done a creditable job educating both the general public and other physicians about the most commonly aspirated foreign materials, including nuts, hot dogs, grapes, and hard candy. In addition, legislation has specified minimum dimensions for components of toys intended for children under 3 years of age, a further mechanism of providing protection for children.

Unfortunately, however, one ubiquitous material has been completely ignored with regard to its potential as a foreign body: the plastic sales tag holder (Fig 1). Recent experience with a 13-month-old child has demonstrated the ability of this radiopaque object to lodge in the subglottis in the anteroposterior direction (Fig 2) and

Fig 1.—Plastic sales tag holder that was aspirated and lodged in subglottis.



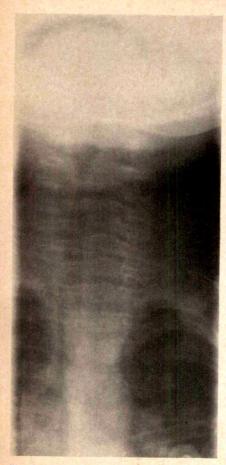


Fig 2.—Anteroposterior neck roentgenogram demonstrating subglottic foreign body.

subsequently produce significant subglottic edema and respiratory compromise. The potential of this object to
cause future similar episodes is unavoidably high: one only has to look
around the floor of any clothing store
or even one's own home to find a potential catastrophe. Though elimination of
the plastic sales tag holder may be an
unrealistic goal, modification of the
object is certainly a viable alternative.
Lengthening of the T-shaped end to at
least 1.5 to 2.0 cm would greatly diminish the risk of aspiration. Retailers,

parents, and physicians should be made aware of this case to effect necessary changes.

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Infantile Myofibromatosis and the Use of Magnetic Resonance Imaging

Sir.—I read the recent report of Moore et al1 with a great deal of interest. These authors described the use of magnetic resonance imaging (MRI) to evaluate and follow the course of an infant with "congenital generalized fibromatosis." My colleagues and I^{2,3} have recently reviewed the disorder in more than 170 infants, and I wish to make several comments. The condition is more aptly termed infantile myofibromatosis (IM).2-5 Approximately half of affected infants will have solitary rather than multiple lesions. In addition, 25% of the children will present after the neonatal period. Finally, the term infantile myofibromatosis emphasizes the dual histopathologic features of the lesions-characteristics of both smooth muscle and fibroblasts.

Infantile myofibromatosis represents the most common fibrous tumor of infancy. In contrast to Moore and colleagues' statement, involvement of IM in the central nervous system has been reported. 4.6.7 Approximately one third of infants with multiple lesions will have visceral involvement. Of these, 75% will die. Without visceral involvement, the prognosis is uniformly good. We are intrigued with the use of MRI in finding "internal" lesions that may not be apparent with other modes of imaging. This technology may be the means by which the course of individual tumors can be

directly monitored. As spontaneous regression is the normal behavior for the lesions of IM, surgical intervention should be reserved for cases in which vital functions are affected. It is hoped that MRI will make this assessment easier.

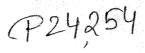
Infantile myofibromatosis is a more common entity than previously believed. Lesions may not be easily discerned and may spontaneously resolve before diagnosis. Unfortunately, the condition is not well known and has been frequently misdiagnosed. Several infants have received chemotherapy for this essentially benign disorder. I concur that the previous subclassifications of IM have not been optimal. However, the classification of the disorder into either single or multiple lesions, with further subdivision based on the presence or absence of visceral tumors, is more acceptable.

The use of MRI has the potential to greatly expand our knowledge about IM. It is important that all physicians who deal with infants be familiar with the clinical manifestations, histopathologic features, and prognosis of affected infants.

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Bone Marrow Examination and Idiopathic Thrombocytopenic Purpura

The need for a bone marrow examination in all children with suspected idiopathic thrombocytopenic purpura (ITP) has been challenged in recent years. By definition, ITP is a diagnosis of exclusion, which means that all known entities that can cause thrombocytopenia have been excluded by a clinical assessment that includes a history, physical examination, and appropriate laboratory tests. There are many diseases that, because of their typical clinical manifestations, do not rely on a bone marrow examination for determining the cause of the thrombocytopenia. Examples include

See also p 508.

hypersplenism, systemic lupus erythematosus, disseminated intravascular coagulation, septicemia, hemolytic-uremic syndrome, and familial thrombocytopenia. Since children with ITP have a typical presentation and course, why have we insisted on bone marrow examinations as part of our routine? After all, the bone marrow morphologic findings are nondiagnostic in ITP. However, it helps subdivide the patients with thrombocytopenia into those with adequate to increased megakaryocytes and those with a hypomegakaryocytic marrow.

The sole reason for the bone marrow examination in ITP is to exclude hypomegakaryocytic thrombocytopenia. Although patients with diseases such as aplastic anemia, the leukemias, marrow replacement with malignant cells, and even the rare congenital hypoplastic anemia have thrombocytopenia, the observed reduced platelet count is virtually always associated with some other hematologic sign, such as anemia, neutropenia, spleno-

megaly, or reticulocytopenia. The thrombocytopenia is rarely the only manifestation in these entities. A blood test that could discriminate between impaired marrow production and excessive peripheral destruction of platelets (similar to the reticulocyte count for red blood cells) could be helpful. Heretofore, no such test has been described. Recently, Steinberg and associates have reported that the plasma levels of glycocalcin may be such an indicator. Glycocalcin is a fragment of glycoprotein Ib of the platelet membrane. Their data suggest that the plasma levels of this protein may reflect overall platelet turnover and depend on platelet mass and destruction. The usefulness of plasma levels of glycocalcin in understanding childhood ITP has yet to be reported. There is no laboratory test that is diagnostic of ITP in children.2 This includes the determination of immunoglobulins on platelets (platelet-associated immunoglobulin), which has a specificity of less than 50%.3

The retrospective study by Halperin and Dovle⁴ in this issue of AJDC and reports by others support the recommendation that a bone marrow examination is not needed in all children with suspected ITP. I would agree that a bone marrow examination must be a component of the diagnostic evaluation if the patient appears atypical for ITP (is less than 1 year of age or has complications such as associated unexplained anemia, neutropenia, reticulocytopenia, splenomegaly, or signs of a chronic illness), and geographic isolation. I disagree with Halperin and Doyle that all patients over the age of 10 years and those who are to receive corticosteroid therapy should undergo a bone marrow examination. For many patients with ITP, especially those with chronic ITP, the disease is detected after the age of 10 years; it is rare to find ITP in children under the age of 1 year. Also, the decision to perform the bone marrow examination should be made irrespective of contemplated therapy. If there exists a fear that therapy may influence the bone marrow morphologic features, then the diagnosis of ITP was not made with confidence. Even intravenous gamma globulin has been purported to be useful in the rare patient with aplastic anemia.⁵

The debate will go on until there is a reliable method for separating hypomegakaryocytic from normohypermegakaryocytic thrombocytopenic disorders. My message to pediatricians and other physicians caring for children is to let the pediatric hematologist decide, keeping in mind that not all children with suspected ITP need a bone marrow examination, irrespective of the bleeding manifestations.

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Ribavirin

Ambivalence About an Antiviral Agent

All of us who care for the young have experienced anxiety and frustration in dealing with hospitalized infants afflicted by respiratory syncytial virus (RSV). The anxiety is particularly great when there is underlying cardiovascular or pulmonary compromise or immunodeficiency, or when the infant is younger than 2 months of age. Frustration occurs because we all wish we could provide something other than supportive care to promptly alleviate the suffering of an infant who is struggling for air and becoming progressively exhausted in the process.

See also p 512.

Over a year ago, ribavirin was released for specific use in such infections. It was heralded as a major advance in definitive treatment of RSV disease, especially among infants who were known in advance to be at risk of death, and perhaps for those who did not possess such risk factors but were nonetheless severely ill.1-3 Ribavirin therapy has not been represented as a great panacea for RSV: the high cost and inconvenience involved in providing aerosol treatment for the better part of each 24-hour period have been among the important considerations in deciding whether a patient should be treated with ribavirin.

Nevertheless, enthusiasm for the effectiveness of ribavirin therapy has been such that many believed that those more desperately ill infants who require intubation and mechanical ventilation might benefit most from this treatment; some clinicians were apparently so convinced that they even regarded this to be a "categorical imperative." As a result, many infants

were treated with ribavirin even before there was Food and Drug Administration approval for its use in this situation. This approach was supported by the American Academy of Pediatrics Committee on Infectious Diseases, with appropriate caveats concerning monitoring and technical aspects, but without details.³

In this issue of AJDC, Outwater and colleagues4 have provided a specific protocol for administration of ribavirin via a pressure-limited ventilator that should reduce, but not necessarily eliminate, the inherent risks. The outlined principles can be applied to other types of ventilators, and they are relatively simple; essentials include close, continuous monitoring, including "one-on-one" nursing care, and regular changes of valves and ventilator tubing. For those who wish to use ribavirin therapy in infants receiving mechanical ventilation, this is an important article that should be shared and discussed with the respiratory therapists and nurses who will be directly involved in the process.

However, there is another important point that needs to be emphasized. Outwater and coworkers wisely make no claims regarding the efficacy of such therapy; furthermore, they suggest that it will be difficult to conduct appropriate trials to determine the efficacy of ribavirin therapy in intubated patients. I hope the latter is not the case.

In a recent commentary, Dr Ellen Wald and colleagues⁵ critically reviewed the reports regarding the efficacy of ribavirin therapy. This, like the article by Outwater and coworkers, is worthy of careful perusal. The essence of their commentary is to appropriately question the enthusiastic acceptance of ribavirin in the treatment of RSV and to ask that further, carefully designed studies be planned

and carried out before we accept it as efficacious.

I would add to this by asking several questions that have concerned me for some time:

- 1. Does ribavirin therapy have clinical efficacy if begun in the later stages of infection? The studies to date have virtually all addressed infants in whom treatment was initiated within three to six days of onset of symptoms. If treatment is begun later and the patient improves, this is often interpreted by the uncritical clinician as evidence that the ribavirin therapy has worked. This may simply be analogous to the "five-day measles effect," in which one initiates therapy with a potent antibiotic on the fourth day of a measles eruption and attributes the improvement over the ensuing two days to that intervention.
- 2. Does ribavirin therapy reduce the need for subsequent intubation and mechanical ventilation? We do not know yet.
- 3. Does ribavirin effectively gain access to the terminal airways when used with a ventilator, or do the intervening tubing and valve alter the particle size and volume of drug that is actually delivered to the critically affected site?
- 4. What is the reasonable duration of therapy? There are as yet no clear guidelines as to when treatment should be discontinued.
- 5. Are there any long-term adverse effects of treatment? I agee that short-term toxicity of ribavirin does not appear to be a serious problem; however, it is a synthetic neucleoside that carries at least theoretical cytotoxic, teratogenic, embryotoxic, and mutagenic risks. We have been somewhat reassured that caregivers who are exposed to the aerosols are probably at little or no risk; however, many advise that pregnant individuals should not

participate in the care of children who are receiving this treatment. Beyond this, we must be aware that adverse effects in the patients, especially the very young, may not become apparent for some years. For example, the fact that repeated exposures to aerosolized ribavirin in a mouse model result in drug accumulation in the brain and cerebrospinal fluid⁶ may be encouraging to those interested in trying such treatment for viral encephalitides but could also be disquieting if we are concerned about potential effects on vulnerable neural cells.

There are other basic biologic and practical questions that readers could add to this list. Some, such as the precise mechanism of drug action on RSV and other viruses and the immunomodulatory effects of ribavirin, are currently being investigated.

The data, the protocols, and the

questions raised here and elsewhere all have to be considered carefully. Like my colleagues, I have agonized over my small, distressed patients and very much wish to help them. However, the balance of cost and risk vs benefit remains uncertain. Greater clarity of foresight is needed, but may not be achieved quickly. For the moment, I suggest that, with regard to ribavirin, we remain agnostics who wish to become believers. We need to continue addressing the questions and realize that it is ethical to insist that the answers be obtained in the best scientific manner possible.

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Heart Surgery

by Jason Byington

Something you see on TV
But they said it would happen to me
I understood why
They told me no lie
But why must it happen to me.

Mostly I felt dread Lying in my bed For this is what they said You will feel pain Enough to drive you insane All this inside my head.

Now that it's over And I'm beginning to recover I think it over After some rest I think it was for the best But I'm sure glad it's over.

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| | Each Entolase- HP Capsule | Each Entolase Capsule |
|---------------------|------------------------------|--------------------------|
| Lipase, USP Units | 8,000 | 4,000 |
| Protease, USP Units | 50,000 | 25,000 |
| Amylase, USP Units | 40,000 | 20,000 |

Amylase, USP Units 40,000 20,000

Inactive Ingredients: Entolase-HP Capsules — cellulose acetate phthalate, corn starch, edible inks, gelatin, iron oxide, povidone, simethicone, sodium chloride, stearic acid, sucrose, talc, titanium dioxide. Entolase Capsules — cellulose acetate phthalate, corn starch, edible inks, gelatin, povidone, simethicone, sodium chloride, stearic acid, sucrose, talc, titanium dioxide.

Clinical Pharmacology: The natural digestive enzymes in Entolase-HP and Entolase Capsules hydrolyze fats into fatty acids and glycerof, split protein into peptides and amino acids, and convert carbohydrates to dextrins and short chain sugars. Under conditions of the USP test method (in vitro), the Entolase products have the following total digestive capacity:

| | Each Entolase - HP Capsule | Each Entolase Capsule |
|------------------------|-------------------------------|--------------------------|
| Dietary Fat, grams | 28 | 14 |
| Dietary Protein, grams | 50 | 25 |
| Dietary Starch, grams | 40 | 20 |
| T (100) | .1 | |

The digestive capacity of a pancreatic enzyme concentrate depends on the amount that passes through the stomach unchanged and is available at the site of action in the small intestine. The pancrelipase in Entolase -HP and Entolase Capsules is contained within enteric-coated microbeads as a safeguard against inactivation of the enzymes in the acid medium

saleguard against inactivation of the enzymes in the acid medium of the stomach.

Indications: Enfolase (Pancrelipase) is indicated in the treatment of exocrine pancreatic insufficiency as associated with but not limited to:

- cystic fibrosis
- post-gastrointestinal bypass surgery
- chronic pancreatitis
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- post-gastrointestinal bypass surgery (e.g., Billroth II gastroenterostomy)
 obstruction of the pancreatic ducts.
- post-pancreatectomy

Contraindications: Do not use in patients hypersensitive to

pork protein.

Precautions: General: Individuals previously sensitized to trypsin, pancreatin, or pancrelipase may have allergic manifestations to the Entolase products.

Information for Patients: Patients should be advised to avoid chewing or crushing the enteric-coated microbeads. Where swallowing of capsules is difficult, capsules may be opened and the enteric-coated microbeads sprinkled over soft food which does not require chewing (e.g., applesauce, gelatin, etc.) and swallowed immediately. Prolonged contact of microbeads with food of pH greater than 5.5 may dissolve the protective enterio

coating:

Carcinogenesis, Mulagenesis, Impairment of Fertility:
Long-term studies in animals have not been performed to
evaluate carcinogenic potential.

Pregnancy Category C: Animal reproduction studies have not
been conducted with the Entolase products. It is also not known
whether these products can cause fetal harm when administered
to a pregnant woman or can affect reproduction capacity.
Entolase products should be given to a pregnant woman only if
clearly needed.

Nursing Mothers: It is not known whether this drug is nutring momens: It is not known whereit into drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Entolase products are administered to a nursing mother.

Adverse Reactions: Extremely high doses of exogenous pancreatic enzymes have been associated with hyperuricemia and hyperuricosuria. Diarrhea or transient intestinal upset

may occur with pancreatic enzyme concentrate. Allergic

may occur with pancreatic enzyme concentrate. Allergic manifestations (see precautions).

Overdosage: Acute toxicity determinations in animals have not been possible since the maximum dose that could be given orally produced no toxic reaction.

Dosage and Administration: The requirement for replacement digestive enzymes varies from patient to patient. To provide dosage flexibility, Entolase is available in two strengths.

Entolase-HP Capsules and Entolase Capsules: One (1) to

Enfolase-HP Capsules and Entolase Capsules: One (1) to three (3) or more capsules with meals as directed by physician depending on patient requirements.

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not refrigerate.
Dispense Entolase-HP Capsules and Entolase Capsules in tight container, preferably with a desiccant.
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Dick Johnson in accounting is having o neart a

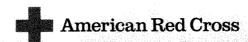
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Leads From the MMWR

Morbidity and Mortality Report Centers for Disease Control, Atlanta

Measles—United States, First 26 Weeks, 1987

Feb 5, 1988 (Vol. 37, No. 4)—FOR THE FIRST 26 weeks of 1987, a provisional total of 2,637 measles cases was reported to CDC by 37 states and 5.6% of the nation's 3,138 counties.* This total is 32.7% less than the 3,921 cases reported for the same period in 1986, when 42 states and 9.0% of the counties reported cases. The overall incidence rate for the first half of 1987 was 1.1 cases per 100,000 population; the rate for the first half of 1986 was 1.7/100.000.

Seven states and New York City accounted for 2,148 (81.5%) of the cases reported for the first 26 weeks of 1987: California reported 647; New York City, 414; New Mexico, 303; Texas, 200; Missouri, 178; New Hampshire, 150; Wisconsin, 139; and Illinois, 117. Incidence rates greater than 3.0/100,000 occurred in New Mexico (22.8), Montana (15.6), New Hampshire (13.2), New York City (5.1), Delaware (4.5), Vermont (4.1), and Missouri (3.6).

CDC's Division of Immunization received detailed information on 2,595 (98.4%) of the 2,637 reported cases. Of these, 2,305 (88.8%) met the standard clinical case definition for measles,** and 723 (27.9%) were serologically confirmed. The usual seasonal pattern was observed—most cases occurred between March and May (weeks 9 to 19).

Fifty-seven (2.2%) of the 2,595 cases were known to be imported from other countries; 30 (52.6%) of these cases occurred among U.S. citizens. An additional 74 cases (2.9%) were epidemiologically linked to imported cases within two generations. Forty-six outbreaks (five or more epidemiologically related cases) accounted for 87.6% of all cases. Five outbreaks of more than 100 cases each accounted for 59.2% of all reported cases.

As in 1986, almost 30% of cases involved children under 5 years of age. Two hundred twenty-five (30.0%) of the 750 preschool-aged patients were less than 1 year of age; 122 (16.3%) were 12-14 months of age; 32 (4.2%), 15 months of age; and 371 (49.5%), 16

months through 4 years of age. The 15- to 19-year age group also accounted for approximately 30% of the cases and was the only age group for which the incidence rate did not decrease between 1986 and 1987. The groups aged zero to 4 years and 15-19 years had the highest incidence rates (4.1/100,000 each); the 10- to 14-year age group had the next highest (3.0/100,000).

Complications were reported in 351 (13.5%) of the 2.595 cases. Otitis media was reported in 175 (6.7%) cases; diarrhea, in 129 (5.0%); pneumonia, in 68 (2.6%); and encephalitis, in 2 (0.1%). Two hundred and one (7.7%) of these patients were hospitalized. Four deaths were attributed to measles, for a death-to-case ratio of 1.5:1,000. All four patients were immunocompromised. Two were 4-year-olds with acquired immunodeficiency syndrome; one was a 9-year-old who had autoimmune hemolytic anemia and was receiving corticosteroid therapy; and one was a 57-year-old with chronic lymphocytic leukemia. Two cases were acquired in the hospital, and two were acquired in the community.

Of the 1,805 (69.6%) patients for whom setting of transmission was reported, 960 (53.2%) acquired measles in primary or secondary schools; 122 (6.8%), in colleges or universities; 386 (21.4%), at home; 114 (6.3%), in medical settings; 31 (1.7%), in day-care centers; and 192 (10.6%), in a variety of other settings including work, church, and the military.

A total of 1,274 (49.1%) patients had been vaccinated on or after their first birthdays. This group included 427 (33.5%) who were vaccinated at 12-14 months of age.*** There were 1,213 (46.7%) unvaccinated patients and 108 (4.2%) with histories of vaccination before their first birthdays.

Of the 2,595 cases, 704 (27.1%) were classified as preventable,² and 1,891 (72.9%), as nonpreventable. Between 1986 and 1987, the absolute number and proportion of preventable cases decreased for all except the over 25-year age group. The highest propor-

tion of preventable cases occurred among persons not of school age-87.5% of cases among adults 25-29 years of age and 68.2% of cases among children 16 months through 4 years of age were preventable. Two hundred sixty-six (37.8%) of the total number of preventable cases involved children 5-19 years of age, and 17.8% of the total cases in this age group were preventable. Cases among adequately vaccinated persons constituted 67.0% of nonpreventable cases and 48.8% of total cases. Of the 1,497 school-aged children who acquired measles, 1,119 (74.7%) had been adequately vaccinated, and 406 (27.1%) had been vaccinated at 12-14 months of age.

Reported by: Div of Immunization, Center for Prevention Svcs, CDC.

CDC Editorial Note: After the record low of 1,497 measles cases in 1983, the number of measles cases increased each year through 1986. The number of cases reported for the first 26 weeks of 1987 is less than that reported during the comparable period in 1986 and reverses this trend. The incidence rates have decreased in all except the 15- to 19-year age group. The increase in this group was attributable to several large outbreaks in secondary schools and colleges.

The four deaths due to measles during the first half of 1987 are the first reported to the Division of Immunization since 1985.8 All four cases either initiated or were part of nosocomial outbreaks involving medical personnel. In addition, a higher proportion of cases were acquired in medical settings in 1987 than in previous years. 4-6 The deaths, combined with the increased proportion of cases acquired in medical settings, highlight the role of these settings in the transmission of measles and emphasize the need for immunization requirements for medical personnel at risk of exposure. 7,8

As in previous years, a large proportion of persons who acquired measles had been vaccinated. In an effort to decrease the occurrence of these cases, changes in the current immunization strategy are being discussed. In many outbreaks, persons vaccinated at 12-14 months of age have been demonstrated to be at slightly higher risk for measles than persons vaccinated at 15 or more months of age. Therefore, the Immunization Practices Advisory Committee (ACIP) recently recommended that revaccination of persons previously vaccinated at 12-14 months of age be considered during outbreaks.8,9 Most cases of measles among persons who received

Table 1.—Reported measles cases and estimated incidence rates* of measles, by age of patients—United States, first 26 weeks, 1986 and 1987

| | | 1986† | | | 1987 | | |
|----------------------|-------|---------|------|-------|---------|------|--------------------|
| Age Group (years) | No. | (%) | Rate | No. | (%) | Rate | Rate Change (%) |
| 0-4 | 1,249 | (32.0) | 7.0 | 750 | (28.9) | 4.1 | (-41.4) |
| 5-9 | 430 | (11.0) | 2.6 | 237 | (9.1) | 1.4 | (-46.2) |
| 10-14 | 1,006 | (25.8) | 5.7 | 500 | (19(3) | 3.0 | (~47.4) |
| 15-19 | 749 | (19.2) | 3.9 | 760 | (29:3) | 4.1 | (+5.1) |
| 20-24 | 243 | (6.2) | 1.1 | 149 | (5:7) | 0.7 | (-36.4) |
| ≥25 | 224 | (5.7) | 0.2 | 199 | (7.7) | 0.1 | (-50.0) |
| Total | 3,901 | (100.0) | 1.7 | 2,595 | (100:0) | 1.1 | (-35.3) |

^{*}Rates per 100,000 population are based on provisional data for both years.

Table 2.—Preventability of measles cases, by age of patients—United States, first 26 weeks, 1986 and 1987*

| 1986† | | 1986† | | | 1987 | | |
|--------------|----------------|-------|---------------|----------------|------|-----------------|--|
| | Tatal | | ntable ses | Taint | | entable ases | |
| Age Group | Total Cases | No. | (%) | Total Cases | No. | (%) | |
| ≤15 mos | 622 | 0 | (0.0) | 379 | 0 | (0.0) | |
| 16 mos-4 yrs | 627 | 533 | (85.0) | 371 | 253 | (68.2) | |
| 5-9 yrs | 430 | 144 | (33.5) | 237 | 41 | (17.3) | |
| 10-14 yrs | 1,006 | 242 | (24.1) | 500 | 79 | (15.8) | |
| 15-19 yrs | 749 | 238 | (31.8) | 760 | 146 | (19.2) | |
| 20-24 yrs | 243 | 174 | (71.6) | 149 | 93 | (62.4) | |
| 25-29 yrs | 88 | 72 | (81.8) | 104 | 91 | (87.5) | |
| ≥30 yrs | 136 | 0 | (0.0) | 95 | 1 | (1.1) | |
| Total | 3,901 | 1,403 | (36.0) | 2,595 | 704 | (27.1) | |

^{*}Based on provisional data for both years.

Table 3.—Classification of measles cases—United States, first 26 weeks, 1987*

| | Cases | | | |
|---------------------------|-------|--------------------------|-----------------|--|
| Classification | No. | (%) of Nonpreventable | (%) of Total | |
| Nonpreventable | | | | |
| <16 Mos. of Age | 379 | (20:0) | (14.6) | |
| Born Before 1957 | 94 | (5∗0) | (3.6) | |
| Adequately Vaccinated | 1,267 | (67)0) | (48.8) | |
| Prior Physician Diagnosis | 10 | (0:5) | (0.4) | |
| Non-U.S. Citizens | 34 | (1.8) | (1.3) | |
| Exemptions | 107 | (5.7) | (4.1) | |
| Medical | (17) | | | |
| Religious | (34) | | | |
| Philosophic | (56) | | | |
| Subtotal | 1,891 | (100.0) | (72.9) | |
| Preventable | 704 | | (27.1) | |
| Total | 2,595 | | (100.0) | |

^{*}Provisional data.

vaccine at 15 months of age or older appear to be the result of primary vaccine failure and not of waning immunity.¹⁰

The two major impediments to measles elimination in the United States—

unvaccinated preschoolers and vaccine failure in the school-aged population require different solutions. Healthcare providers should take advantage of every opportunity to vaccinate these children.¹¹ Measles-containing vaccines should be administered to eligible children regardless of the need for other vaccines. The ACIP now recommends simultaneous administration of MMR, DTP, and OPV at 15 months of age, 12 both routinely and for children behind on their immunization schedules.

The number of vaccine failures among children 5-19 years of age has stimulated efforts to devise strategies to reduce the rate of primary vaccine failure. CDC is convening a group of consultants to review the current status of efforts to eliminate measles in the United States and to discuss potential modifications¹⁸ to the current strategies. These modifications include revaccination, either routinely, as a two-dose schedule, or selectively, as part of outbreak control.

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[†]Estimated total excludes 20 reported cases for which the age group was unknown.

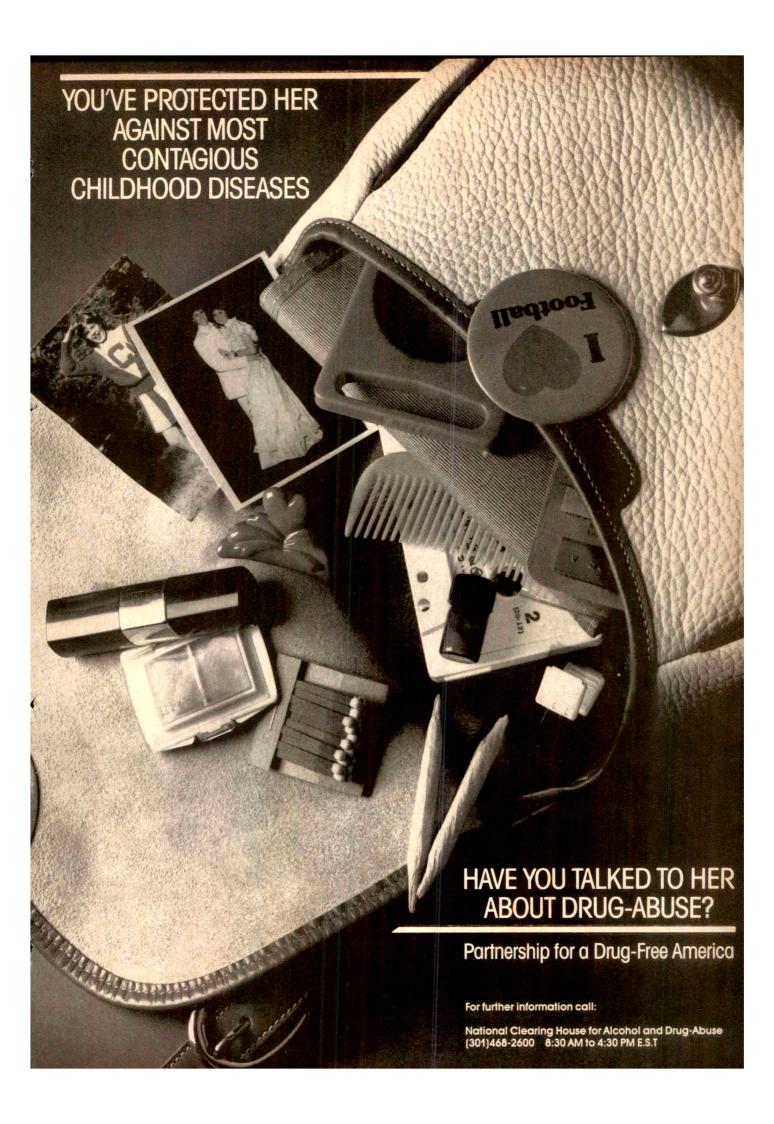
[†]Preventability was unknown for 20 cases in 1986.

^{*}A provisional total of 3,588 was reported for all of 1987.

^{**}Fever 38.3 degrees C (101 degrees F) or higher, if measured; generalized rash lasting 3 or more days; and at least one of the following: cough, coryza, or conjunctivitis

coryza, or conjunctivitis.

***Includes two adequately vaccinated patients
who were born before 1957 and five who were
less than 16 months of age.



The Editorial Board Speaks . . .

Ben H. Brouhard, MD





We detailed Ben's educational history and his past and current accomplishments in the February 1986 issue.1 Since that time, he has been asked to broaden his editorial responsibilities in two areas: (1) a computer-based pediatric journal and (2) a journal involved with diabetes, a disease that has been of interest to him professionally for many years. He is presently sponsoring a Kempner Fellow in Pediatric Endocrinology, and he has received grants for the investigation of dietary protein intake in diabetes and diabetic nephropathy both in animal models and in children with the disease. Ben has been named to the American Academy of Pediatrics Task Force for Topics for Annual Review for the PREP program. He was selected as a National Institutes of Health site visitor for their General Clinical Research Centers Division in December 1987. He was selected for membership on the steering committee of the Computer Learning Resource Center and the search committee for the director of the Endocrinology Division of the Department of Internal Medicine, both at the University of Texas Medical Branch, Galveston. Ben is also currently chairperson of the executive council of the Department of Pediatrics at the University of Texas Medical Branch. Despite all of these efforts, he continues to publish actively in the scientific literature and to assist AJDC in his capacity as Editorial Board member and constant reviewer.

BETTER TREATMENT FOR CHILDREN WITH DIABETES BUT NO CURES YET

As a pediatrician, I frequently am asked "When will there be a cure for diabetes?" Ten years ago, with the success of pancreas transplants, I was predicting that in about ten years we would have a cure for diabetes. I am now more cautious in making such predictions, but I do remind parents and teenagers who ask this question how far we have come in the last decade.

Ten years ago, insulin therapy usually consisted of one shot per day of insulin (an intermediate-acting insulin with or without regular). Encouraged by what were then provocative new data, we began recommending conversion from one to two shots per day of insulin to improve blood glucose control throughout a 24-hour period and to prevent progression of diabetic retinopathy. Most parents did not want to subject their children to another shot. However, patients who adopted the new regimen found that it allowed more flexibility in the timing of meals, and they also physically felt so much better that none returned to one shot per day. Today, we routinely prescribe two shots per day for all patients beginning to receive insulin, and sometimes three shots per day. Insulin regimens today can be as varied as the life-styles of the people who use them, including intermediate-acting, regular, and long-acting insulins and, in specific instances, the subcutaneous insulin infusion pump. All of these methods provide good blood glucose control along with more flexibility in life-styles to accommodate the needs of diabetic children with two working parents or diabetic teenagers and college students with different schedules depending on the day of the week.

The other major area that has seen great improvements in the last ten years has been the monitoring of blood glucose concentrations. The technologic advance that has allowed blood glucose monitoring in the home is the development of a lancet that punctures the skin rather than slicing it. This technique has made obsolete the measurement of urine sugar excretion as an indicator of the blood glucose level. It allows tighter and more precise blood glucose control than monitoring urine sugar measurements. The use of home blood glucose monitoring has led to the development of strips to measure accurately the blood sugar level and a multitude of devices to read the

strips. These machines not only read the strips for blood glucose concentrations but also can save the readings for recall; when used with the proper computer program, these machines can deliver the blood glucose values in any number of combinations and permutations in numerical or graphic form. This is a particularly attractive option for teenagers, who may dutifully perform the blood glucose tests but "forget to write them down." The ability to accurately measure and control blood glucose levels has been a significant advance in the treatment of the pregnant diabetic and can virtually eliminate the complications that affect the infant by normalizing blood glucose levels during pregnancy.

Other areas of research have extended our ability to care for patients with the complications of diabetes. The importance of controlling hypertension in patients with diabetes has been recognized in the last several years. The potential importance of decreasing dietary protein intake and the use of angiotensin-converting enzyme inhibitors to preserve renal function in patients with early diabetic nephropathy are currently being studied.

The advances of the past decade significantly extend our ability to treat and monitor the child with insulin-dependent diabetes. They improve the quality of life and provide physical well-being, making it possible to achieve better blood glucose control. They may also reduce the risk of long-term microvascular complications. These control and measurement techniques will require that probabilities concerning the development of complications in patients with diabetes be reevaluated. Data currently available were generated when urine testing and one shot per day of insulin were the predominant forms of therapy. The improvements in the ability to control and monitor blood glucose levels do not, however, decrease the need for insulin injections and for frequent blood glucose monitoring. Thus, although a cure for every diabetic has not been achieved in the last ten years, there have been significant advances in the care of the child with diabetes. We hope that in the next ten years a cure or cures will become feasible.

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*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride Supplementation: Revised Dosage Schedule Pediatrics 63(1):150-152, 1879.

*The Committee lavors initiating fluoride supplementation shorth after birth in breast-fed infants (0.25 mg F/day). In formulia-fee infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula.

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| 0.25 mg TRI-VI-FLOR | Drops | 50 ml Bottle | 0.25 |
| 0.25 mg with Iron TRI-VI-FLOR | Drops | 50 ml Bottle | 0.5 |
| 0.5 mg TRI-VI-FLOR 1.0 mg | Tablets | Bottle of 100 | 1.0 |

1.0 mg
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Perspectives on the Relative Resurgence of Mumps in the United States

Stephen L. Cochi, MD; Stephen R. Preblud, MD; Walter A. Orenstein, MD

· Although the United States has enjoyed great success in the control of mumps since the licensure of live virus mumps vaccine in 1967, a relative resurgence of mumps during the 1986-1987 period has raised concerns about the long-term effectiveness of mumps vaccine. We reviewed mumps surveillance data, historical information on mumps vaccine distribution and recommendations for its use, survey data on levels of mumps immunization in US children during the 1973-1985 period, the effect of mumps immunization school laws on the reported incidence of mumps among states with and without such laws, and studies of mumps vaccine effectiveness. Following licensure, a decade elapsed before mumps vaccine was endorsed as a routine immunization of childhood, while immunization survey and vaccine distribution data reflected only gradual acceptance of the vaccine. However, mumps incidence declined during this period, resulting in a rela-

The United States has made great

since the licensure of live virus mumps

vaccine in December 1967. Subse-

quent administration of more than 80

million doses of mumps vaccine in this

country has had a dramatic impact on

the reported incidence of mumps. In

1985, an all-time low of 2982 cases was

reported, representing a 98% de-

crease from the 152 000 cases reported

in 1968, the year mumps became a

strides in the control of mumps

now between 10 and 19 years old. Mumps immunization school laws offer an approach to deal with the problem of continuing susceptibility in school-age populations. (AJDC 1988;142:499-507)

tively underimmunized cohort of chil-

dren born between 1967 and 1977 who

grew up during a period when the risk

of exposure to mumps was rapidly de-

clining. The resurgence of mumps since

1986 has been characterized by a selec-

tive increase in incidence and a shift in

the age group at highest risk to middle

and high school students in those states

lacking comprehensive mumps immu-

nization school laws. Postlicensure field

evaluations of mumps vaccine effective-

ness have not demonstrated waning

vaccine-induced immunity. The data in-

dicate that the relative resurgence of

mumps in the United States is chiefly

due to a failure to vaccinate all suscep-

tible persons, especially those who are

nationally notifiable disease (Fig 1). Since 1986, however, we have experienced a relative resurgence of mumps in the United States. Numerous outbreaks have occurred in older school-age children, on college campuses, and in other young adult populations. There has been a revival of interest in mumps and mumps vaccine among those not accustomed to having to deal with mumps outbreaks. In addition, the occurrence of mumps in vaccinated persons has predictably raised concerns about the effectiveness of mumps vaccine in the minds of the lay public, the press, and the public health community.

Why is mumps on the rise again, like a modern-day Lazarus raised from the dead? Leaving aside the possible contribution of improved reporting of mumps in recent years, which is difficult to assess in the absence of pertinent information, this report will address other possible explanations for the surge in reported mumps activity. Fundamentally at issue is whether the increase in mumps is a result of vaccine

failures, or a failure to vaccinate susceptible persons. We are not able to evaluate this issue directly because vaccination status of mumps cases is not routinely reported. However, indirect measures can shed some light. To begin to get some insight into which of the alternative hypotheses is the primary explanation, it is useful to review the history of recommendations for use of mumps vaccine, the historical pattern of mumps vaccine use in the United States, and surveillance data documenting the changing epidemiology of mumps in the United States.

METHODS Recommendations for **Mumps Vaccine Use**

We reviewed all statements issued by the Immunization Practices Advisory Committee (ACIP) of the US Public Health Service regarding the recommended use of live virus mumps vaccine in age-specific and risk groups. 1-5

Mumps Vaccine Distribution

Data on net distribution of doses of live virus mumps vaccine in the United States were reviewed for the period 1968-1986. These data were compared with annual net distribution of live virus measles and rubella vaccines. Net distribution was considered to be equivalent to gross annual sales or distribution less recorded returned doses. Civilian and military data were combined.6

US Immunization Survey

The US Immunization Survey (USIS) was conducted annually from 1965 to 1985 by the Bureau of the Census in cooperation with the Centers for Disease Control (CDC), Atlanta. Immunization data were collected by the Bureau through a supplemental questionnaire attached to the monthly Current Population Survey. The estimates were based on data obtained in a

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From the Division of Immunization, Center for Prevention Services, Centers for Disease Control. Atlanta.

Reprint requests to Technical Information Services, Center for Prevention Services, Centers for Disease Control, Atlanta, GA 30333.

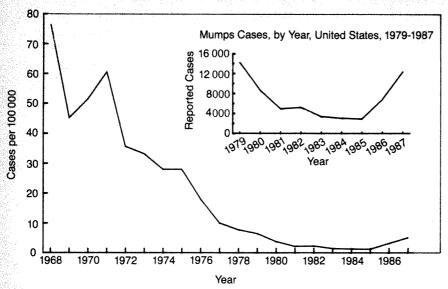


Fig 1.—Reported mumps incidence, United States, 1968 to 1987 (1987 provisional data).

subsample of households interviewed for the Current Population Survey.7 The USIS was a random probability survey seeking information regarding the immunization status of the members of selected households. Information on mumps immunization status of persons 1 to 14 years of age was obtained during 1973 to 1985. Beginning in 1979, data on persons 15 to 19 years of age were also collected. From 1979 to 1985, approximately one third of the total sample, designated the "record sample," was based on information reported by a parent from a written immunization record obtained from a private physician, a health department clinic, or a military facility.8

Mumps Surveillance

Mumps was first placed on the list of nationally notifiable diseases in 1922. It was deleted from the list in 1950, then reinstated after mumps vaccine was licensed in December 1967. From 1968 to 1976, the CDC received weekly reports of mumps cases from the health departments of each of 52 reporting areas (50 states, the District of Columbia, and New York City). From 1977 to 1979, 51 areas reported; in 1980 and 1981, 50 areas reported; and since 1982, only 48 areas have reported (Mississippi, New Mexico, Oklahoma, and Oregon do not report mumps cases to the CDC). Age data were not reported from more than 50% of total nationally reported cases until 1981. Case reports originating from physicians, nurses, and other health professionals are reported to local and state health authorities and then to the CDC. In the absence of a uniform clinical case definition, the CDC accepts any case reported as mumps, with or without laboratory confirmation. Therefore, it is possible that some of the cases reported are actually not mumps infections. Although there is no precise estimate of the proportion of mumps cases reported in the United States, it is likely that reported incidence rates substantially underestimate the actual occurrence of cases.⁹

Mumps Immunization School Laws

Reported mumps incidence among states with and without mumps immunization school laws was analyzed for 1985 and 1986. 10 States with school laws were further stratified into those that comprehensively include kindergarten through grade 12 ("K-12 law") and those with a school entry (generally covering kindergarten and first grade) or other type of regulation that does not comprehensively include kindergarten through grade 12 ("partial law"). State population estimates for 1985, by age, from the Bureau of the Census were used to calculate age-specific incidence rates of mumps. 11

RESULTS Chronology of ACIP Recommendations

Although mumps vaccine was licensed in December 1967, the public health community considered mumps control of low priority. The ACIP stated at that time that "mumps immunization should not be allowed to compromise the effectiveness of public health programs of already established importance" (Table 1). Despite the licensure of combined measles-

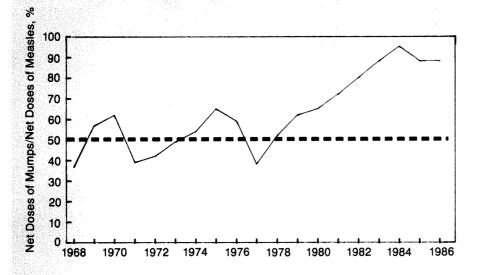
| the ACI | 1.—Recommendations of P on Use of Mumps Vaccine in the United States* |
|---------|---|
| Year | Target Groups (Categories Are Additive) |
| 1967 | Not for routine use in children "Consider" for use in children approaching puberty, adolescents, adults |
| 1972 | "Of particular value" in children approaching puberty, adolescents, adults |
| 1977 | All children after 12 mo of age |
| 1980 | MMR is preferred for routine use in children Vaccinate susceptible children, adolescents, adults unless contraindicated |

*ACIP indicates Immunization Practices Advisory Committee; MMR, measles, mumps, rubella.

mumps-rubella (MMR) vaccine in 1971, the ACIP reaffirmed its recommendation in 1972, largely for reasons of cost (the mumps component makes up slightly more than one half the cost of MMR vaccine), that mumps prevention was of lower priority than "more essential ongoing community health activities." It was not until late in 1977 that the ACIP first began to recommend routine use of mumps vaccine in children 12 months of age or older. By 1980, MMR was recommended as the preferred vaccine for routine use in children, and a more aggressive approach to the vaccination of susceptible older children and young adults was advocated.2-5 The more aggressive approach was supported by benefitcost analyses showing that \$7 to \$14 were saved for every dollar spent on mumps control. 13,14

Mumps Vaccine Distribution

In keeping with the chronology of recommendations for use of mumps vaccine, the net distribution of mumps vaccine was substantially below that of both measles and rubella vaccines before 1981, varying between 37% and 65% of the net doses of measles vaccine distributed (Fig 2, top). During this period, net annual distribution of mumps vaccine gradually increased from 1.96 million doses in 1968 to 5.21 million doses in 1980. Since 1983, the annual net distribution of mumps vac-



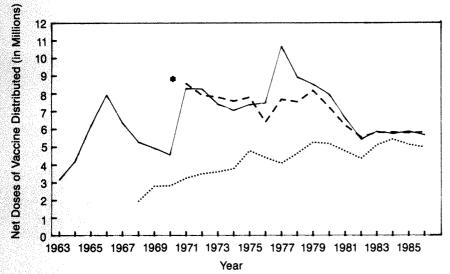


Fig 2.—Net distribution (in millions of doses) of live virus measles (straight line), mumps (dotted line), and rubella (dashed line) vaccines, United States, 1963 to 1986. Asterisk indicates 29.3 million net doses of rubella vaccine were distributed in 1970.

cine has stabilized at between 5.0 million and 5.5 million doses (Fig 2, bottom). This amount has represented between 88% and 95% of measles vaccine doses annually distributed during the 1983-1986 period, and between 86% and 94% of rubella vaccine doses annually distributed during the same period (Fig 2, top).

Trends in Age-Specific Levels of Mumps Immunization, 1973-1985

While data from the USIS may not be accurate enough to determine precisely the actual immunization levels, the comparability of the survey from year to year makes the data useful to assess temporal trends (Fig 3). Mumps vaccine coverage did not reach levels

above 50% in any age group until 1976 (5- to 9-year-olds), and in persons 15 to 19 years of age until 1983. The prevalence of mumps vaccination among school-age children has lagged the most in high school students, followed by middle school and elementary school students. There is evidence that the gap in mumps immunization levels observed between elementary and middle school students has gradually closed, presumably due to the movement toward routine use of MMR in preschool children beginning in the mid-1970s (Fig 3). The current population of 15- to 19-year-olds was too old, however, to have benefited substantially from this change in policy and practice. These historical patterns of mumps vaccine use have resulted in the accumulation of a pool of susceptible persons among older school-age children and young adults.

Additional data from the USIS show that the school-age population of 5- to 19-year-olds has had historically lower mumps immunization levels compared with measles and rubella vaccines. This gap has gradually been closing with routine use of MMR vaccine in the cohort of preschool children in recent years.

Mumps Surveillance

Although the reported occurrence of mumps has declined by at least 90% in all age groups since licensure of the vaccine,15 until recently mumps has remained a disease of young schoolage children, with the highest reported risk of disease occurring in children 5 to 9 years of age (Fig 4). This pattern was similar to that observed during the prevaccine era.16,17 Although the proportion of remaining mumps cases occurring in persons 15 years of age or older steadily increased to slightly more than 50% of reported cases during the 1981-1985 period, the magnitude of disease in this population markedly decreased between 1967 and 1985.15

In 1986, the United States began to experience a relative resurgence of mumps (Fig 1). A total of 7790 mumps cases was reported, more than 2.5 times the number of cases reported in 1985. Two states, Illinois and Tennessee, alone accounted for more than one half of all reported cases. Furthermore, more than 12 200 mumps cases were provisionally reported in 1987.

The relative increase in reported mumps in 1986 compared with the previous two years disproportionately affected infants too young to be vaccinated and persons 10 to 19 years of age (Table 2). These age groups experienced 3.5-fold to 4.4-fold increases in the reported incidence of mumps in 1986 compared with 1984. The attack rates in 10- to 14-year-olds exceeded the attack rate in 5- to 9-year-olds, and the attack rate in 15- to 19-year-olds nearly equaled that in 5- to 9-year-olds. Such a shift in risk from 5-to 9-year-olds to older persons has

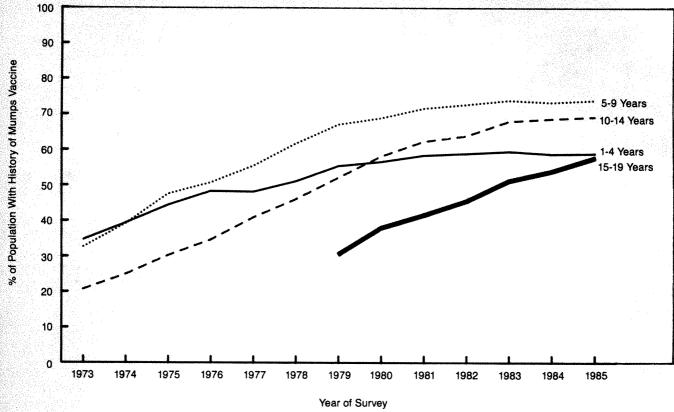


Fig 3.—Estimated mumps vaccine coverage by age group, US Immunization Survey, 1973 to 1985, total sample.

been observed only once before during the mumps vaccine era, in 1982, and the shift in that year was substantially less pronounced.¹⁸

The shift in age-specific attack rates of mumps has also begun to extend into the college-age population. Three states reported outbreaks of mumps with a total of 480 cases in colleges and universities during the 1986-1987 academic year. ¹⁹ An unprecedented outbreak in excess of 100 cases among young adults has been reported in a workplace setting in Chicago during the fall of 1987 (Karen Kaplan, MD, CDC, written communication, Nov 18, 1987).

Effect of Mumps Immunization School Laws

A major contributing factor to the changing age pattern of mumps in the United States has been the institution of mumps immunization school laws. School laws passed during the latter part of the 1970s and during the 1980s have resulted in focal changes in the epidemiology of mumps that vary from state to state. When the ACIP first recommended mumps vaccine rou-

tinely for all children in 1977, five states had mumps immunization school laws. That number had increased to 22 states by 1980, and to 31 states (including one state that currently does not report mumps nationally) by 1983. By 1986, 15 of the 46 states that report mumps nationally still did not require proof of mumps immunity for school entry. Of the 31 states that did require mumps immunization, 11 had laws that affected only first entry to school (generally kindergarten or first grade), six had laws that affected children beyond first grade but did not comprehensively include kindergarten through grade 12, and 14 states required proof of mumps immunity for all students in kindergarten through grade 12.

In 1985, the incidence rate of mumps in states with no law was twice that of states with a comprehensive K-12 school law (Fig 5). In 1986, the rate was 12-fold higher in states without a law, and 2.6-fold higher if Illinois and Tennessee are excluded from the analysis because of their unusually high incidence of mumps. Of note, the reported mumps incidence rate during

1985 and 1986 in states with only a partial law (ie, a school entry law or other law not comprehensively including kindergarten through grade 12) was no different than that in states with no school law, if Illinois and Tennessee are again excluded. This may be due to the fact that, in recent years, most preschool US children have routinely been getting mumps protection as part of MMR vaccine, regardless of whether a school law was or was not in effect, and such children now make up most of the current highly immune cohort of elementary school students.

The shift in the age group at highest risk during 1986 was not a uniform observation across all states, and was affected by state immunization regulations (Fig 6). States with K-12 laws did not experience a change in the pattern of age-specific attack rates and continued to have the usual peak attack rates in 5- to 9-year-olds, although these rates were substantially lower than in states without comprehensive laws. The states with peak mumps attack rates in 10- to 19-year-olds were those that either lacked

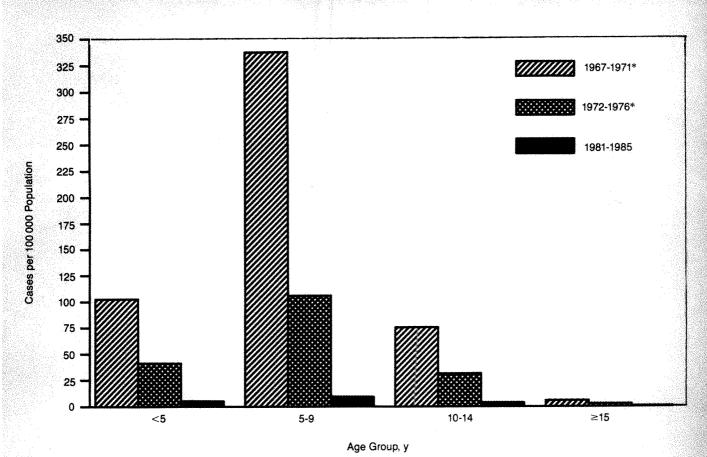


Fig 4.-Average annual mumps incidence rates by age group, United States, 1967 to 1985. Asterisk indicates California, Massachusetts, New York City only. Age-specific data were not available for US totals until 1977.

mumps immunization school laws or states that did not have comprehensive K-12 laws. Since there is no reason to believe that mumps vaccine failure or waning vaccine-induced immunity should be a problem confined only to states without K-12 laws, a more likely explanation for both the increase in mumps cases and the change in pattern of age-specific incidence would be a failure to vaccinate all persons at risk in those states lacking comprehensive mumps immunization school laws. Furthermore, attack rates of mumps were markedly elevated in infants, preschool children, and young school-age children in states lacking mumps immunization school laws as compared with states with such laws (Fig 6), suggesting widespread transmission of mumps to remaining susceptible persons in all age groups in states without mumps laws.

COMMENT

Although the United States has enjoyed great success in the control of mumps since the licensure of live virus

mumps vaccine in 1967, the relative resurgence of mumps during the 1986-1987 period has been a cause of concern. Several lines of evidence suggest that the increase in reported mumps cases is primarily the result of a failure to vaccinate susceptible persons and not the result of vaccine failures. National immunization policy historically was slow to endorse mumps vaccine as a routine immunization of childhood. Thus, a decade elapsed between licensure of the vaccine in 1967 and the recommendation at the end of 1977 that it be given routinely to all children. The sluggish pattern of mumps vaccine distribution during this decade is further evidence that the vaccine only gradually came into widespread use. During the decade following the licensure of mumps vaccine, however, the incidence of reported mumps cases declined markedly. Presumably, this was a result of the incremental uptake of sufficient mumps vaccine in the US population to interrupt substantially the transmission of mumps virus. Data from

secondary attack rate studies and mathematical models show that clinical mumps is substantially less communicable than measles, leading to reductions in transmission of mumps at immunization levels that would have only minimal impact on measles transmission.20,21 Consequently, a cohort of children born between about 1967 and 1977 (ie, persons between 10 and 20 years of age in 1987) grew up during a period when the chance of exposure to wild mumps virus as a preschool or young school-age child was markedly declining while the opportunity to receive mumps vaccine was uncertain. To a lesser extent, those born during the decade preceding licensure of the vaccine (ie, persons between 20 and 29 years of age in 1987) had some diminished exposure to wild mumps virus during their childhood, compared with those born prior to 1957 (ie, persons ≥30 years of age in 1987). The latter group reached adolescence before availability and use of mumps vaccine began to alter the epidemiology of mumps by interrupting trans-

Table 2.—Age Distribution of Reported Mumps Cases and Estimated Incidence Rates*—United States, 1984-1986

| | | 1984 | | | 1985 | | | 1986 | į. | | |
|--------------------------------|------|---------|-------|------|---------|------|------|---------|-------|-------------------------|--|
| Age Group, y | No | . (%) | Rate* | No | . (%) | Rate | No | . (%) | Rate* | Rate Ratio 1986:1984 | |
| <1 | 37 | (1.4) | 1.2 | 29 | (1.1) | 0.9 | 142 | (2.0) | 4.2 | 3.6 | |
| 1-4 | 364 | (13.7) | 2.9 | 339 | (13.1) | 2.7 | 569 | (8.0) | 4.3 | 1.5 | |
| 5-9 | 842 | (31.7) | 5.9 | 837 | (32.5) | 5.7 | 1768 | (24.7) | 11.1 | 1.9 | |
| 10-14 | 771 | (29.1) | 5.0 | 649 | (25.2) | 4.4 | 2625 | (36.7) | 17.3 | 3.5 | |
| 15-19 | 335 | (12.6) | 2.0 | 405 | (15.7) | 2.4 | 1535 | (21.5) | 9.0 | 4.4 | |
| 20-24 | 79 | (3.0) | 0.4 | 83 | (3.2) | 0.5 | 177 | (2.5) | 0.9 | 2.3 | |
| 25-29 | 60 | (2.3) | 0.3 | 66 | (2.6) | 0.4 | 84 | (1.2) | 0.4 | 1.3 | |
| ≥30 | 166 | (6.3) | 0.2 | 163 | (6.3) | 0.1 | 246 | (3.4) | 0.2 | 1.4 | |
| Total, known age | 2654 | (87.9) | | 2571 | (86.2) | | 7146 | (91.7) | | | |
| Total, unknown age | 367 | (12.1) | | 411 | (13.8) | | 644 | (8.3) | | | |
| Total No. of Cases Reported | 3021 | (100.0) | 1.3 | 2982 | (100.0) | 1.2 | 7790 | (100.0) | 3.2 | 2.5 | |

*Cases per 100 000 population (projected census data) extrapolated from the age distribution of patients with known age to total cases. Not adjusted for states not reporting mumps (Mississippi, New Mexico, Oklahoma, Oregon).

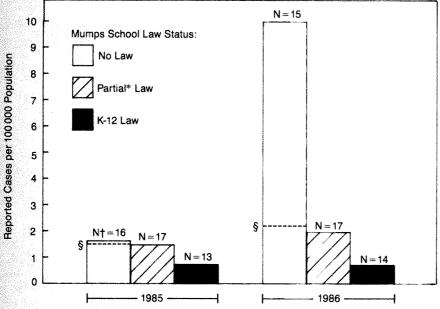


Fig 5.—Reported mumps incidence among states with and without mumps immunization school laws, United States, 1985 to 1986. Asterisk indicates affecting some school children but not comprehensively including kindergarten through grade 12 (K-12); N†, number of states (District of Columbia is included with K-12) (mumps is not notifiable in four states); section mark, excludes Tennessee and Illinois.

mission of the virus within the United States.

In short, the gradual uptake of mumps vaccine during the decade following its licensure resulted in a relatively underimmunized cohort of children now 10 to 19 years of age who were born between 1967 and 1977, a period when the risk of exposure to mumps was rapidly declining. Because the greater mobility of older children and teenagers increases the potential for contact among susceptible persons, this has led to mumps outbreaks when disease is introduced in these populations. There is reason to believe, then, that a bulge in susceptibility exists within this age group that did not exist in the same age group during the prevaccine era. To our

knowledge, there are, unfortunately, no mumps serologic studies conducted since the 1970-1973 period to address this issue.²² Such studies would provide an estimate of the actual susceptibility burden and enhance our current understanding of the epidemiology of mumps.

At the same time, the movement toward routine use of mumps vaccine in children born since 1977 was gradual. Although increasing use of combined MMR vaccine and the enactment of mumps immunization school laws by 26 states between 1977 and 1986 led to higher levels of mumps immunization in US children, the timing of these events varied among the 50 state immunization projects and multitudinous private providers of vaccine. The gradual implementation of these changes likely resulted in isolated pockets of susceptible unvaccinated children now 5 to 9 years of age.

Although available information suggests that failure to vaccinate is the major cause of the current national epidemic of mumps, the possibility that mumps vaccine failures may have also contributed needs further evaluation. Questions exist concerning the duration of mumps vaccine-induced immunity and efficacy under conditions of day-to-day use. Controlled, randomized clinical trials prior to vaccine licensure demonstrated 95% to 96% efficacy (Table 3).23,24 However, the longest period of follow-up in these studies was only 20 months. Serologic studies have shown that both neutralizing antibody and protection against clinical mumps have persisted for at least 12 years after vaccination.25 These data suggest that immunity is long term and probably lifelong.

Recent field evaluations of vaccine effectiveness during mumps outbreaks have generated somewhat lower estimates for vaccine efficacy that range from 75% to 91%. 26-31 These studies are still consistent with the clinical trial results if one looks at the upper bounds in the confidence intervals of the point estimates. However, the lower-than-expected point estimates of mumps vaccine effectiveness raise some concern about the level of long-term clinical protection conferred by the vaccine. On the other hand,

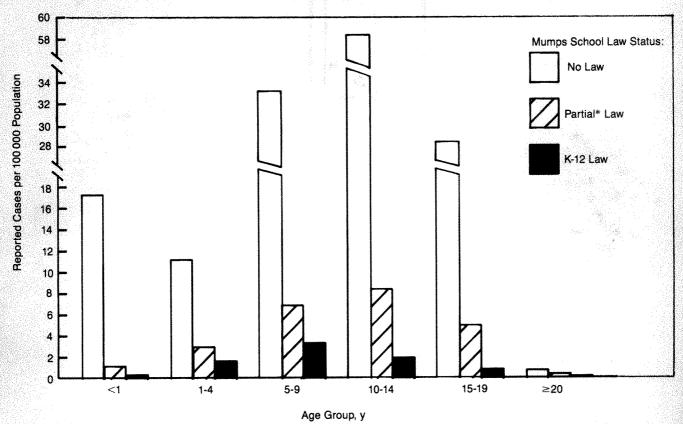


Fig 6.—Reported age-specific mumps incidence among states with and without mumps immunization school laws, United States, 1986. Asterisk indicates affecting some school children but not comprehensively including kindergarten through grade 12 (K-12).

| Table 3.—Published Clinical Studies of Mumps Vaccine Efficacy | | | | | | | |
|---|-----------|----|-------------------------------|---------------|--|--|--|
| Study Population | Year | Ef | accine ficacy, 95% CI)* | | | | |
| Clinical trials Philadelphia | 1965-1967 | 95 | (88-98) | | | | |
| North Carolina | 1966-1967 | 96 | (88-98) | | | | |
| Outbreak studies | | | | | | | |
| New York | 1973 | 79 | (53-91) | #421 <u>6</u> | | | |
| Canada | 1977 | 75 | (49-87) | | | | |
| Ohio | 1981 | 81 | (71-88) | | | | |
| Ohio | 1982 | 85 | (39-94) | | | | |
| New Jersey | 1983 | 91 | (77-93) | | | | |
| Tennessee | 1986 | 78 | (65-86) | | | | |

^{*}CI indicates confidence interval.

none of these studies has suggested that waning vaccine-induced immunity was a factor leading to the outbreak.

Although low calculated vaccine efficacy may be the result of true low efficacy, the methodology used in post-licensure field evaluations of vaccine effectiveness has limited our ability to

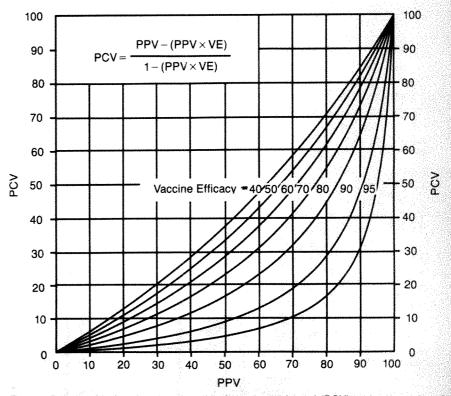


Fig 7.—Relationship between percentage of cases vaccinated (PCV) and percentage of population vaccinated (PPV) for seven different percentage values of vaccine efficacy (VE) (from Orenstein et al⁴⁷).

draw firm conclusions about the reasons for the somewhat lower estimates for vaccine efficacy compared with the clinical trials. Kim-Farley et al29 demonstrated that errors in methodology such as an inaccurate case definition, incomplete surveillance with limited case ascertainment, and inaccurate determinations of vaccination status were all factors that potentially contributed to falsely low estimates of vaccine efficacy in observational studies. Since acute parotid swelling can occur from a variety of causes, ideally serologic or viral isolation studies should be undertaken in such investigations to ensure the accuracy of the case definition. 32-39 The type of serologic testing performed is critical since complement fixation or standard hemagglutination inhibition (HI) may not be reliable compared with enzymelinked immunosorbent assay, neutralization antibody, or "sensitive" HI tests. The complement fixation and HI tests are less sensitive and are less specific due to cross-reacting antibodies to other paramyxoviruses. 32-34,40-46 A further limitation has been that the more reliable antibody tests have not been widely available. The occurrence of serologically confirmed mumps cases in vaccinated persons is also predictable, as with any vaccine of less than 100% efficacy. This problem becomes more prominent as vaccine coverage increases. Although the overall rate of susceptibility decreases, there will be an increasing proportion of remaining susceptible persons and hence cases occurring in vaccinated persons even when the vaccine efficacy is high47 (Fig 7). Incomplete case ascertainment with selectively better identification of vaccinated compared with unvaccinated cases may result in vaccine efficacy estimates that are biased downward. Prior mumps disease and subclinical infection occurring before the outbreak or a lack of comparable levels of exposure of vaccinees and nonvaccinees to mumps virus during the outbreak can potentially confound the analyses. Finally, inaccuracies in determining mumps immunization status from parent histories or school records may result in misleadingly low estimates of efficacy. 27,29,31,47

The effectiveness of mumps immunization school laws in decreasing mumps incidence has been consistently demonstrated. 9,15,30,48-50 Future policy emphasis should include enforcing existing laws requiring vaccination against mumps, extending present laws to comprehensive kindergarten through grade 12 coverage, and considering the introduction of laws requiring vaccination for all students in kindergarten through grade 12 in states without an existing law. The occurrence of a cluster of outbreaks of mumps illness on university campuses during the 1986-1987 period underscores the need for preadmission immunization requirements that include mumps vaccine.19 The recommendation of the American College Health Association that all college health programs require documentation of previous mumps disease or vaccination for entering students should be followed.51

The data presented indicate that the relative resurgence of mumps in the United States appears to be chiefly due to a failure to vaccinate all susceptible persons, especially those who are now between 10 and 19 years old, and, to a lesser extent, those now of college age. Seroepidemiologic data to either confirm or disprove this supposition are needed. The lack of evidence of waning vaccine-induced immunity from mumps vaccine is reassuring, but additional carefully conducted epidemiologic studies to evaluate mumps vaccine effectiveness will be needed to monitor this situation. Mumps immunization school laws that are enforced have been clearly shown to be an effective means of mumps prevention and offer an approach to deal with the problem of continuing susceptibility in school-age populations.

We are now experiencing the movement of mumps outbreaks through older age groups than we have been accustomed to observing in the past. We have outlined the reasons why we think this phenomenon is taking place. The stage is set for considering efforts to ensure that older school-age children and those entering college have been vaccinated against mumps if such outbreaks are to be prevented in the future.

Dick Bruce, Division of Immunization, CDC, provided the information on state immunization requirements, and Don Eddins, Division of Immunization, CDC, provided data from Biologics Surveillance and the USIS.

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CORRECTION

Incorrect Terminology.—In the article entitled "Pediatric Acquired Immunodeficiency Syndrome: Neurologic Syndromes," published in the January 1988 issue of AJDC (1988;142:29-35), errors occurred on pages 33 and 34. On page 33, the second sentence in the second paragraph of the "Comment" section should have read as follows: "Complications included CNS lymphoma, cerebrovascular [not cardiovascular] accident, and CNS infection caused by conventional and opportunistic pathogens." The sentence in the same paragraph beginning at the bottom of page 33 and continuing on page 34 should have read as follows: "Not surprisingly, a rapidly progressive encephalopathy heralded by mental status changes and seizures occurred in children with lymphoma and cerebrovascular [not cardiovascular] accident."

Is Bone Marrow Examination Justified in Idiopathic Thrombocytopenic Purpura?

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 Bone marrow examination is widely accepted among pediatric hematologists as a mandatory investigation in childhood idiopathic thrombocytopenic purpura (ITP). The aim of this procedure is to confirm the presence of megakaryocytes and to exclude other conditions, such as leukemia and aplastic anemia. To assess the need for bone marrow examination, we reviewed the charts of 127 children with presumed ITP and found that bone marrow examination led to a different diagnosis in five (3.9%) of them. All five patients had presented with clinical and/or laboratory features atypical of acute ITP; none had leukemia. The initial clinical and laboratory findings of 50 patients with aplastic anemia also were reviewed; all had features atypical of acute ITP. Proper history and physical examination as well as a compiete blood cell count are reliable means of recognizing patients with typical vs atypical features of ITP. Bone marrow aspiration could be limited safely to those patients with atypical features of ITP or to patients being treated with corticosteroids.

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Acute idiopathic thrombocytopenic purpura (ITP) is one of the most common hematologic disorders among pediatric patients. It usually occurs in healthy 2- to 10-year-old children of either sex^{1,2} and frequently follows a viral infection. The onset of the disease is abrupt and usually consists of

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petechiae, bruises, and, less frequently, epistaxis.³ There is almost invariably no history of symptoms or signs such as weight loss, fatigue,

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pallor, decreased appetite, or recurrent fever. Physical examination most often reveals mucocutaneous petechiae and bruises, but lymph nodes, liver, and spleen are not enlarged (the tip of the spleen may occasionally be palpable), and the patient appears to be in good general condition. In addition, the complete blood cell count is normal, except for the thrombocytopenia, the severity of which is variable.^{2,4}

Based on these clinical and basic laboratory features, and provided no unusual characteristics confuse this picture, ITP should be readily diagnosed in most instances, without the need for more invasive diagnostic procedures.

In practice, however, and probably more so in teaching institutions, it has been a strong tradition to confirm the clinical diagnosis by examination of the bone marrow. This, characteristically, shows normal cellularity, with a normal to an increased number of megakaryocytes and normal maturation of erythroid and myeloid lineages. These features allow the exclusion of other causes of thrombocytopenia, such as leukemia, aplastic anemia, or congenital amegakaryocytic thrombocytopenia.

Despite this tradition and the fact that most authoritative pediatric and hematology textbooks present bone marrow examination as a mandatory step in the workup of ITP,⁵⁻⁷ some authors have recently questioned the justification for this procedure. ^{1,8,9} We present further data to support a non-invasive approach to managing these patients.

METHODS

All bone marrow examination requisitions that were sent to the Hematology Laboratory of The Hospital for Sick Children (HSC), Toronto, from Jan 1, 1984, until May 15, 1987, were reviewed to determine which were motivated by the suspicion of ITP. Most requisitions were labeled as follows: "? ITP," "thrombocytopenia," "acute onset of petechiae and bruises," or "low platelets; rule out leukemia." A few did not mention any provisional diagnosis, but review of the corresponding charts ascertained that the bone marrow aspirate was requested to confirm the diagnosis of acute ITP.

The number of cases where acute ITP was confirmed was compared with the number of other diagnoses found on bone marrow examination. We further reviewed the chart of each patient for which discordance was found between the presumptive clinical diagnosis and the actual hematopathologic diagnosis. This review was done to verify whether the clinical presentation of these patients was typical of acute ITP or, conversely, whether clinical clues alone (such as age, history, physical assessment, or initial blood cell count) might have been indicative of another cause of the throm-bocytopenia.

All cases of acquired or constitutional aplastic anemia diagnosed at this institution over a ten-year period (1978 to 1987) were also reviewed. Salient clinical features and the initial blood cell counts were recorded. By definition, the blood cell count was considered abnormal (and tentatively incompatible with ITP) if, in addition to the thrombocytopenia, the hemoglobin value was less than 100 g/L (<10 g/dL), the total white blood cell count was less than 5×10^9 /L ($< 5 \times 10^3$ /mm³), the absolute neutrophil count was less than 1.5×10°/L (<1500/mm³), or the mean corpuscular volume was greater than 94 fL after the age of 3 months.

RESULTS

A total of 2062 bone marrow specimens were examined over the study period, an average of approximately 600 per year. Among those, 132 (6.4%) were aspirated from 127 patients to

Table 1.—Bone Marrow Aspirations Performed at The Hospital for Sick Children,
Toronto (1984 to 1987), to Confirm ITP*

| Trail | No. of Bone Marrow Aspirations | | | | | |
|-------|--------------------------------|---------------|-------------------|-----------------|--|--|
| Year | Total | ITP Confirmed | Inadequate Sample | Other Diagnosis | | |
| 1984 | 39 | 36 | 1 | 2 | | |
| 1985 | 38 | 31 | 4 | 3 | | |
| 1986 | 37 | 37 | 0 | 0 | | |
| 1987† | 18 | 18 | 0 | 0 | | |
| Total | 132 | 122 | 5 | 5 | | |

^{*}ITP indicates idiopathic thrombocytopenic purpura.
†Jan 1 to May 15.

| Table 2.—Summary of Findings in Patients Whose Bone Marrow Examinations Initially Failed to Confirm ITP* | | | | | | | |
|--|--|---|---|--|--|--|--|
| Patient No. | Acute ITP, Typical on Clinical Grounds | Diagnosis Based on First (Second) [Third] Bone Marrow Examination | Final Diagnosis | | | | |
| 1 | No | Inadequate specimen (ITP, eosinophilia) | Wiskott-Aldrich syndrome | | | | |
| 2 | No | ITP, dyserythropoiesis | Chronic ITP, dyserythropoiesis | | | | |
| 3 | Yes | Possible aplastic anemia (Biopsy-determined ITP) | ITP | | | | |
| 4 | No | Inadequate specimen (amegakaryocytosis) | Transient thrombocytopenia associated with trisomy 21 | | | | |
| 5 | No | Inadequate specimen (amegakaryocytosis) | Amegakaryocytosis, possible aplastic anemia | | | | |
| 6 | No | Inadequate specimen (inadequate specimen) [ITP] | Chronic ITP | | | | |
| 7 | No | Amegakaryocytosis | Amegakaryocytosis | | | | |

^{*}ITP indicates idiopathic thrombocytopenic purpura.

confirm a provisional diagnosis of ITP. As shown in Table 1, 122 (92.4%) of these clearly confirmed this diagnosis, whereas ten samples (actually corresponding to seven patients) failed to do so.

Five of these ten bone marrow samples were judged as inadequate for diagnosis because of the absence of fragments or the presence of clots or crush artifacts. In each of these cases, a bone marrow aspiration was repeated to obtain a specimen suitable for examination. In two cases (patients 1 and 6), the repeated bone marrow examination findings were felt to be consistent with ITP, although in patient 1, Wiskott-Aldrich syndrome was eventually diagnosed. Table 2 summarizes the diagnoses of these seven patients. As is illustrated by the following short case reports, it is noteworthy that only one child (patient 3)

had a clinical presentation typical of acute ITP; indeed, after some doubts raised by his first bone marrow examination, this diagnosis was confirmed by a repeated bone marrow aspiration. All other patients presented with characteristics unusual enough to elicit consideration of alternative diagnoses.

Between July 1, 1978, and June 30, 1987, 50 cases of acquired or constitutional aplastic anemia were diagnosed at HSC. Thirty-four patients had idiopathic aplastic anemia, 11 had Fanconi's syndrome, and five had other forms of marrow failure.

As shown in Table 3, none of these children presented with isolated thrombocytopenia. Although five patients were referred with a presumptive diagnosis of ITP, all of them had easily recognizable abnormalities that should have raised the possibility of

Table 3.—Initial Laboratory and Clinical Features of Patients With Aplastic Anemia (N = 50)

| | No. (%) of Patients |
|--|------------------------|
| Unusual age for childhood ITP | |
| (<1 year or >10 years) | 15 (30) |
| Total white blood cell count | |
| $<5 \times 10^9/L (<5 \times 10^3/mm^3)$ | 36 (72) |
| Absolute neutrophil count | |
| <1.5×10 ⁹ /L (<1500/mm ³) | 39 (78) |
| Hemoglobin level <100 g/L | |
| (<10 mg/dL) | 31 (62) |
| Mean corpuscular volume | 00 (50) |
| >94 fL | 28 (56) |
| Abnormal physical findings* Patients presenting with | 12 (24) |
| No abnormalities | 0 (0) |
| One abnormality | 1 (2) |
| Two abnormalities | 12 (24) |
| Three abnormalities | 19 (38) |
| Four or more abnormalities | 18 (36) |
| Patients presenting with one | |
| or more abnormalities of | |
| complete blood cell count | |
| (in addition to | |
| thrombocytopenia) | 49 (98) |

*For example, dysmorphic features, growth retardation, cutaneous and skeletal abnormalities, and microcephaly.

another diagnosis: two had obvious physical anomalies characteristic of Fanconi's syndrome, were anemic and neutropenic, and had a markedly increased MCV; the other three were all neutropenic at presentation, and two of them also had a low total white blood cell count in addition to their thrombocytopenia. Ironically, one of these patients had an initial diagnosis of ITP based on the bone marrow examination. She was found to have a profoundly hypocellular marrow on subsequent aspiration. Only one patient had no hematologic abnormalities other than thrombocytopenia. This patient's condition, however, could not be mistaken for a typical case of ITP since he was 41/2 months old at time of diagnosis and exhibited several physical features of Fanconi's syndrome. His platelet count was 118×10^{9} /L (118×10^{3} /mm³), rather than the more common profound thrombocytopenia of ITP.

PATIENT REPORTS

PATIENT 1.—A 9-month-old male infant presented with a four-month history of bruising. Results of a bone marrow aspiration done at the referring hospital were consistent with ITP, although there was a marked eosinophilic granulocytosis. The

infant also had a history of eczema and recurrent episodes of diarrhea. On admission at HSC, the platelet count was $17.0 \times 10^9/L$ ($17 \times 10^9/mm^3$). A repeated bone marrow sample was inadequate for diagnosis. A third aspirate showed a normal number of megakaryocytes and marked eosinophilia. Results of a further immunologic workup were consistent with the diagnosis of Wiskott-Aldrich syndrome.

PATIENT 2.—An 8-year-old boy was referred to HSC for investigation of recurrent ITP. A first episode had occurred at 5 years of age, at which time a good response to prednisone had been noted. On this occasion, the patient was found to be steroid dependent. Bone marrow examination showed many megakaryocytes, but dyserythropoietic changes were noted, the origin of which has not been elucidated.

Patient 3.—A 10-year-old boy presented with a history typical of acute ITP. Blood cell counts were normal, except for the platelet count, which was 9.0×10^9 /L (9×10^9 /mm³). The bone marrow was considered hypocellular, with a decreased number of megakaryocytes. A bone marrow biopsy was performed a few days later, which showed only mild hypocellularity and normal maturation of all three cell lines. A good response to short-term steroid treatment was observed, and the patient has remained well since.

PATIENT 4.—Thrombocytopenia was diagnosed in a 2-day-old male infant affected with trisomy 21. At birth, the infant had respiratory distress due to a "wet lung" syndrome, and required ventilation for a few hours. His mother's platelet count was normal, whereas his ranged from 11.0×10^9 /L to 14.0×10^9 /L (11×10^3 /mm³ to 14×10³/mm³) before transfusion of a unit of random donor platelets, to which he responded well. The first bone marrow aspiration yielded an inadequate specimen. A repeated aspirate was obtained, which showed a decreased number of megakaryocytes. Subsequent platelet counts normalized within ten days and since have remained in the normal range.

Patient 5.—A 1-year-old female infant presented with a three-month history of petechiae and bruises. She had no congenital abnormalities. Her hemoglobin level was normal, but she had combined thrombocytopenia, with a platelet count of 25×10^9 /L (25×10^9 /mm³), and neutropenia, with a neutrophil count of 1.0×10^9 /L (1×10^9 /mm³). The first bone marrow aspirate was inadequate for diagnosis, while the second revealed moderate hypocellularity and a markedly decreased number of megakaryocytes. Chromosomal studies yielded normal results. She failed to respond to steroid therapy and a year later

showed a progressive decrease in hemoglobin value. No suitable donor has been identified for bone marrow transplant.

PATIENT 6.—A female infant was admitted at 1 year of age with acute onset of petechiae. The initial blood cell count showed a platelet count of 9.0×109/L (9×103/mm3), a hemoglobin level of 94 g/L (9.4 g/dL), and a normal white blood cell count. The bone marrow examined at the referring hospital was described as "hyperproliferative." The patient did not respond to steroid therapy and was transferred to HSC because of a sudden fall in hemoglobin level. Physical examination revealed enlarged liver and spleen (3 and 2 cm, respectively, below the costal margin). Antinuclear factor was not detectable, but the direct antiglobulin test result was positive with fraction C3d of complement detectable on the red blood cells. Chromosomal studies also showed an unexplained high frequency of breakages. The first two bone marrow samples were inadequate for examination; the third showed a normal number of megakaryocytes, consistent with ITP. She subsequently had a slow, transient response to prednisone therapy but later suffered a relapse and eventually underwent splenectomy at 18 months of age.

Patient 7.—An 18-year-old man with Klinefelter's syndrome, tetralogy of Fallot, mental retardation, scoliosis, and paraplegia (secondary to a cardiac arrest) was found via a routine blood cell count to be mildly thrombocytopenic, with a platelet count of $92.0 \times 10^9/L$ ($92 \times 10^3/mm^3$). This, in retrospect, had already been noticed over the past eight years, with platelet counts ranging from $90.0 \times 10^9/L$ to $140.0 \times 10^9/L$ ($90 \times 10^3/mm^3$ to $140 \times 10^9/L$ mm³). The bone marrow showed normal cellularity, with megakaryocytic hypoplasia.

COMMENT

In an editorial comment, Lilley-man¹º pointed out that the diagnosis of ITP "is essentially made by exclusion, and to avoid delayed or inappropriate treatment the more sinister conditions such as leukemia, marrow hypoplasia, and consumption coagulopathy should be dismissed at the outset. To this end a bone marrow aspirate, preferably with a trephine biopsy, and a disseminated intravascular coagulation screen are minimal initial investigations together with careful examination of the peripheral blood."

This position seems to be shared by most pediatric hematologists in North

America, as suggested by a survey conducted among 322 specialists. According to this survey, 74% of these physicians would routinely perform a bone marrow aspiration in a child presenting with typical features of acute ITP. The major reasons for performing the bone marrow aspiration included the following: to rule out leukemia (78%), to rule out aplastic anemia (51%), to alleviate parental anxiety (46%), and to respond to the referring physician's expectations (20%).

Anxiety over missing a diagnosis of acute leukemia or aplastic anemia obviously appears to be the most powerful motivation to perform a bone marrow aspiration in children with presumed acute ITP; but is this anxiety really justified? In the estimated 4200 years of experience accumulated by this group of physicians, only five patients were found to have leukemia and only 11 were found to have aplastic anemia instead of the clinically presumed ITP. Moreover, as no data were given regarding the particular features of these misdiagnosed patients, one cannot exclude the possibility that some, if not most, of them had clinical characteristics suggestive of their true diagnosis. This hypothesis is strengthened by McIntosh's⁸ observation that isolated thrombocytopenia is not a presenting feature of acute leukemia; of 218 children with leukemia, 22 had no peripheral blast cells on their initial blood film; of these, only seven had platelet counts below $50.0 \times 10^9/L$ $(50 \times 10^3/mm^3)$, and of these seven, only one had a normal neutrophil count. However, the latter patient had a hemoglobin level of 50 g/L (5.0 mg/dL) and hepatosplenomegaly.

Similarly, our review of 50 cases of aplastic anemia demonstrates that thrombocytopenia is not an isolated finding in this condition, whether acquired or congenital. Indeed, 98% of these patients had at least one additional abnormality in their complete blood cell count, and the single patient who had isolated thrombocytopenia also had clinical features that would be considered very atypical of childhood ITP.

Taking a reverse standpoint, we pro-

vide further evidence that acute ITP indeed can be safely diagnosed on clinical grounds and with the help of a complete blood cell count as the only mandatory laboratory investigation (perhaps along with a basic coagulation screen, although the risk of missing a consumption coagulopathy, as suggested by Lilleyman, 10 remains to be demonstrated).

Among the 127 patients who were recognized over a 3.5-year period as possible cases of ITP, only three (patients 4, 5, and 7) would have been misdiagnosed had a bone marrow aspiration not been performed. All three patients had amegakaryocytosis; in one it was transient, in one it was chronic, and in another it slowly progressed toward pancytopenia. In fact, none of them would have suffered any delay in diagnosis or treatment since they all presented with such unusual features of ITP that a bone marrow aspiration in these cases would not be a matter of controversy. In three other patients (patients 2, 3, and 6), whose initial bone marrow examinations did not permit the confirmation of ITP, acute or chronic ITP was diagnosed on the basis of a repeated aspirate and/ or the clinical evolution. The dyserythropoiesis of patient 2 was a coincidental finding that confused the issue of ITP but had no practical impact on the management of this child. As for patient 1, the bone marrow examination results were compatible with ITP (despite the eosinophilia), and the final diagnosis of Wiskott-Aldrich syndrome was based on clinical and immunologic evidence.

Finally, in this series, not a single case of acute leukemia was mistakenly diagnosed as ITP.

Although bone marrow aspiration cannot be considered a risky procedure, it certainly is a painful and frightening experience, one to which children should be submitted only if they are likely to benefit from it. All other justifications, such as alleviating parental anxiety (a synonym, in our view, of physician's anxiety) or responding to the referring physician's expectations, seem ethically unacceptable. On the other hand, there is now enough evidence,1,8,9 in addition to our own data, to show that the chances of mistaking leukemia or aplastic anemia for ITP are extremely small, provided serious attention is given to the clinical information available and to the peripheral blood films.

We therefore conclude that bone marrow examination need not be routinely performed in children with good clinical evidence of acute ITP. Rather, it should be reserved for those cases where age (<1 to 2 years, >10 years), history, physical assessment, or peripheral blood cell count are atypical of classical acute ITP. Should steroids be contemplated for treatment, we would still agree that a preliminary bone marrow examination is indicated. This latter safeguard will prevent the rare case of a child with an evolving picture of leukemia from being given what would constitute inappropriate therapy. This, however, may not necessarily apply to intravenous gamma globulin therapy, which has become, in many institutions, including ours, the initial therapy preferred for the treatment of acute ITP. It is also conceivable that certain circumstances, such as geographic isolation, could necessitate bone marrow examination at the time of hematologic consultation. This would allow the primary care physician to initiate steroid therapy at a later date, without reconsultation.

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Ribavirin Administration to Infants Receiving Mechanical Ventilation

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· Aerosolized ribavirin was administered to 12 infants with bronchiolitis who were receiving mechanical ventilation. All patients had a history of cardiac or pulmonary disease and developed severe respiratory failure during their infection. We developed a method for ribavirin administration and patient monitoring that included timed circuit valve and tubing changes to avoid obstruction by precipitated drug, frequent endotracheal tube suctioning, and constant observation of the patient and ventilator. All patients were successfully treated. We conclude that ribavirin can be safely administered to infants receiving mechanical ventilation.

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Bronchiolitis, an acute pulmonary infection often due to respiratory syncytial virus (RSV), is a common cause of acute respiratory failure in infancy. Children less than 3 months of age and those with underlying cardiac, pulmonary, or immunologic disorders are at particular risk for severe respiratory tract disease or even death

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due to this virus. Until recently, there has been no specific therapy for the treatment of RSV-induced bronchiolitis.

Ribavirin is a synthetic nucleoside approved by the Food and Drug Administration for the treatment of RSV infections in infants. Several randomized, controlled studies have shown a statistically significant improvement in certain clinical factors, such as arterial oxygen tension, when ribavirin is administered by aerosol to normal infants with RSV infections.⁴⁶ A less severe clinical course has also been reported in RSV-infected patients with underlying cardiac or pulmonary diseases when treated with ribavirin aerosol.⁷

Recently, the American Academy of Pediatrics suggested that infants requiring mechanical ventilation because of RSV infection may be most likely to benefit from ribavirin therapy and acknowledged the technical difficulties and need for constant patient monitoring.⁸ Ribavirin therapy is not approved (as of this writing) for administration to infants receiving mechanical ventilation because of concern about drug-crystal deposition at various sites in the ventilator tubing, the endotracheal tube, and the exhalation valve.

Although two studies of ribavirin use have included patients receiving ventilation, 7.9 details concerning patient monitoring and maintenance of the ventilation circuit have not been published for the clinician. In this article, we document the clinical course of 12 infants requiring mechanical ventilation who received aerosolized ribavirin, present our method of ribavirin administration to these infants, and describe our approach to patient monitoring.

PATIENTS AND METHODS Patients

Infants at high risk for severe RSV infection (premature infants or those with congenital heart disease or chronic lung disease), who presented with symptoms of viral bronchiolitis or pneumonitis and required mechanical ventilation, were treated with ribavirin (after informed consent was obtained from the parents). A solution of

20 mg of ribavirin per milliliter of water was aerosolized and administered continuously for 20 hours a day via a pressure-limited ventilator. Nasal washing specimens were obtained from each infant and examined for RSV antigen by standard immunofluorescent techniques. 10

Ventilator Circuit and Small-Particle Aerosol Generator (SPAG) Unit

A schematic view of the circuit through which ribavirin was administered via a pressure-limited ventilator in our intensive care unit is shown in the Figure. We used the Healthdyne 102 infant ventilator (Healthdyne Inc, Marletta, Ga), but the technique can be adapted to certain other pressure-limited ventilators. The SPAG unit (Viratek, ICN Pharmaceuticals, Costa Mesa, Calif) that delivered the ribavirin consists of a nebulizer, a drug reservoir flask, a drying chamber, and a gas flow meter for both the nebulizer and the drying chamber. The SPAG unit was connected by a T-piece to the inspiratory limb of the ventilator between the humidification system and the patient.

The SPAG unit was powered by a high-pressure blended gas source with the same fraction of inspired oxygen that the patient was to receive. Once the SPAG unit was connected, flow from the nebulizer was set at 6 L/min, and the ventilator flow was then adjusted to obtain the desired peak inspiratory pressure. It was usually necessary to reduce or discontinue the drying chamber flow to remain within the desired peak inspiratory pressure limit.

Adult-sized (rather than infant-sized) tubing was used in the circuit in the first nine patients to reduce the chance of obstruction due to drug precipitation. We have subsequently used pediatric tubing (Intec Medical Inc, Blue Springs, Mo) in three patients and have not had problems with drug precipitation in the tubing. The tubing was changed every eight hours.

A one-way valve in the inspiratory limb proximal to the connecting T-piece prevented ribavirin from entering the humidifier or the ventilator. A one-way valve

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between the SPAG unit and the T-piece in the inspiratory limb of the ventilator prevented loss of volume to the SPAG unit. The one-way valves (No. 1644, Hudson Oxygen Therapy Sales Co, Temecula, Calif) were changed every four hours. The exhalation valve (Hospitak Inc. Lindenhurst. NY) is disposable and was changed every four hours, regardless of the amount of precipitate present.

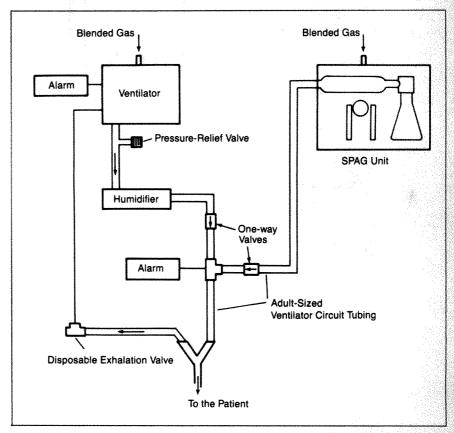
The entire system was examined every two hours. Temperature was maintained at 36°C to 37°C to decrease risk of drug precipitation. In addition to the ventilator alarm, a second high- and low-pressure alarm (Healthdyne Series 1000 Pressure Alarm, Healthdyne Inc) was connected to the inspiratory limb of the circuit. This was a safeguard to warn of occlusion of the primary ventilator alarm tubing or of any inadvertent circuit disruption.

Patient Care and Monitoring

Patients were treated only in the intensive care unit, and each patient was the sole responsibility of one nurse every shift to ensure close monitoring during ribavirin administration. Nurses and house officers were instructed as to the importance of constant observation of both the patient and the ventilator. This included evaluation of chest-wall excursion during the respiratory cycle and ventilator monitoring for changes in peak inspiratory pressure or positive end expiratory pressure. Any change in these pressures of more than 2 mm Hg from the set pressure was an indication for examination of the entire circuit. The endotracheal tube was instilled with physiological saline and cleared at least every two hours to ensure patency. Each patient was continuously monitored by pulse oximetry. In addition to these modifications, management of intubated patients was carried out as previously reported.11

RESULTS

During a 12-month period (1986 through 1987), 12 intubated infants were treated according to this protocol (Table). Three infants had congenital heart disease: patient 1 had a ventricular diverticulum; patient 2 had a double-outlet right ventricle, with a recently repaired aortic coarctation; and patient 12 had an atrioventricular canal defect. Patient 3 had trisomy 21, cardiomyopathy, and hypoplastic lungs. Patient 4 had trisomy 21 and a chronic lung disease of uncertain origin. Seven patients had bronchopul-



Ventilator circuit adapted for ribavirin delivery (Healthdyne 102 infant ventilator and Healthdyne Series 1000 Pressure Alarms [Healthdyne Inc, Marletta, Ga]). SPAG indicates small-particle aerosol generator.

monary dysplasia. All but one of the latter patients were dependent on oxygen before occurrence of infection. and one was ventilator dependent.

All 12 patients were successfully treated with ribavirin aerosol for four to ten days while receiving mechanical ventilation. Eight patients had documented RSV infection. In six of these infants, infection resolved clinically after a single course of therapy. Two infants required re-treatment when their RSV infection did not resolve and clinical symptoms recurred.

Three patients required a peak inspiratory pressure greater than 36 mm Hg (38 to 45 mm Hg) while receiving ribavirin. The remaining nine infants received adequate ventilation, with a peak inspiratory pressure of 25 to 36 mm Hg.

All patients survived their acute respiratory failure. There were no adverse side effects noted, and all patients tolerated ribavirin therapy well. Six patients were discharged from the hospital, including two patients who

had experienced severe multiple organ failure concurrent with respiratory insufficiency (one of whom improved sufficiently to undergo cardiac transplantation). Three patients remain hospitalized. Three patients, only one with a documented RSV infection. subsequently died of unrelated causes. ten days, 16 days, and nine weeks after ribavirin therapy, respectively.

COMMENT

We have shown that safe and effective ribavirin therapy can be provided to critically ill infants receiving mechanical ventilation when intensive nursing and respiratory care is available. Our protocol requires one nurse for each patient, frequent suctioning of the endotracheal tube, and constant vigilance in observing both the patient and the ventilator.

Respiratory therapy management includes frequent examination of the ventilator and circuit as well as timed valve and circuit changes. Flows through the generator and the venti-

| Patient No./ Age, mo | Diagnosis | RSV Immunofluorescence | Duration of Ribavirin Therapy, d | Highest PIP/PEEP, mm Hg | Outcome |
|-------------------------|--|---------------------------|--|----------------------------|--|
| 1/7 | Ventricular diverticulum, cardiogenic shock | + | 5 | 30/5 | Survived, eventually underwent cardiac transplantation |
| 2/7 | Complex congenital heart disease, cardiogenic shock, liver and renal failure | . + | 10 | 45/7 | Survived, discharged home |
| 3/3 | Trisomy 21, hypoplastic lungs, severe pulmonary hypertension, cardiomyopathy | | 5 | 35/7 | Died 15 days after admission of cor pulmonale |
| 4/6 | Trisomy 21, chronic lung disease | + | 8 | 32/5 | Survived, discharged home |
| 5/11 | BPD, ventilator dependent 1st course | + | 6 | 32/5 | Survived RSV infection, died 16 days later of cor |
| | 2nd course | + | 4 | 32/5 | pulmonale |
| 6/6 | BPD, ventilator dependent | - | 5 | 29/7 | Survived, discharged home |
| 7/2 | BPD | | 5 | 38/5 | Died nine weeks later of unrelated causes |
| 8/6 | BPD | + | 7 | 25/5 | Survived, discharged home |
| 9/3 | BPD, hypoplastic lungs, oxygen dependent | + | 5 | 40/5 | Survived, discharged home |
| 10/5 | BPD | - | 5 | 30/5 | Survived, doing well in hospital |
| 11/10 | Hypoplastic lungs, BPD | + | 5 | CPAP 3 | Survived, doing well in hospital |
| 12/5 | Atrioventricular canal defect | | | 36/5 | Survived, being weaned from |
| | 1st course | + | 5 | | ventilator |
| | 2nd course | + | 5 | | |

*RSV indicates respiratory syncytial virus; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; plus sign, positive; minus sign, negative; BPD, bronchopulmonary dysplasia; and CPAP, continuous positive airway pressure.

lator must be carefully adjusted to avoid exceeding the desired peak inspiratory pressure due to the additional flow from the SPAG unit. The drying-chamber flow may be set at a low rate or turned off to avoid delivering excess pressure. This does not affect drug delivery.9

We did not observe drug precipitation on valves or in the tubing in any of our patients. However, because of previously reported complications, we feel it would not be wise to extend the time interval between valve and tubing changes. The use of one-way valves on the inspiratory line and frequent expiratory valve changes may account for the absence of drug deposition in our series. A second high- and low-pressure alarm for the inspiratory limb of the circuit provides an added safeguard.

This ventilator circuit and SPAG unit can be adapted to some other pressure-limited ventilators (eg, Bourns BP 200 or Bourns Bear Cub [Bear Medical Systems Inc, Riverside, Calif] or Sechrist IV-100B [Sechrist Industries Inc, Anaheim, Calif]). The addition of a disposable

exhalation valve prevents possible damage from ribavirin entry into the ventilator. Adding additional flow (the SPAG unit) to some of the newer ventilators equipped with extra safety mechanisms may be difficult and should be tested before patient use.

We have experimented with a number of different filters placed in the expiratory limb to reduce environmental exposure of personnel to ribavirin; however, we have not found a satisfactory filter. In the high temperature and humidity of the system, the filters rapidly became damp, which resulted in ribavirin deposition, obstruction of gas flow, and inadvertent positive end expiratory pressure. Demers et al9 did not report these problems with filter obstruction, perhaps because their use of heated internal wire tubing allowed them to maintain the necessary temperature and humidity without condensation in the tubing. In this system, the filters were necessary to protect the ventilator from ribavirin deposition, whereas in our system, filters would be used only to protect health care personnel from exposure. The limited data available

suggest that short-term exposure of personnel to ribavirin is not toxic. 12 Teratogenic potential is not known; however, we are looking at the safety and economic feasibility of using heated internal wire tubing and filters in our system.

Other differences between our protocol and that reported by Demers et al⁹ include our use of two one-way valves in the inspiratory limbs of the circuit and our more rigorous ventilator-circuit maintenance schedule. Demers et al do not discuss patient care or monitoring in their report.

It was not the intent of this study to evaluate the efficacy of ribavirin in intubated patients with severe bronchiolitis and/or pneumonitis. In fact, it will be difficult to conduct controlled randomized trials of ribavirin efficacy in intubated patients because of the considerable differences in the clinical status of such patients. However, all 12 of the high-risk patients described herein (eight with documented RSV infection) survived their infection, as did 16 patients receiving ventilation described by Hall et al. We believe that, using the approach described

herein, ribavirin can be safely administered to selected infants while they are receiving mechanical ventilation.

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Book Review

Hematology of Infancy and Childhood, ed 3, vol 1, 684 pp, with illus, \$38.50, Hamilton, Ill, Drug Intelligence Publications Inc, 1987.

The base of information needed for a contemporary understanding of pediatric hematology, both in terms of its theoretical infrastructure as well as its practical clinical aspects, continues to expand rapidly. This now-classic text is firmly established as the main repository of this fund of information, and the newly released third edition is a welcome updating of this work.

Hematology of Infancy and Childhood has continued to be produced as a two-volume set. Most of the chapters have been thoroughly revised from the previous edition, with the entire volume being expanded by only approximately 100 pages. Despite its substantially increased price, which might well relegate this work mainly to libraries, a distinctly poorer-quality high-glare paper has unfortunately been substituted, with noticeable deterioration, especially in the clarity of reproduction of the figures and photomicrographs.

The authors who contributed to Hematology of Infancy and Childhood are among the foremost authorities in pediatric hematology, and the work clearly reflects the state of the art in each of the major areas of this pediatric discipline. As often occurs with multiauthored works, there is fair amount of overlap from chapter to chapter (eg. virtually identical charts showing the developmental progression of the globin chains appear in three different chapters), and the treatment given to different topics sometimes varies considerably. An excellent chapter on "The Platelet: Quantitative and Qualitative Abnormalities," for example, is 135 pages long, whereas those chapters dealing with all of the hematologic malignant neoplasms (including the leukemias, lymphomas, and lymphohistiocytic disorders) are encompassed in 107 pages. Although the latter sections are current and well written, the reader seeking an extended discussion of these topics would more likely prefer to consult the corresponding sections in *Clinical Pediatric Oncology* (St Louis, CV Mosby Co, 1984). Certainly, one of the most valuable parts of the book for the clinician is the set of tables at the end of volume 2, which list normal hematologic values of infants and children.

A book of this size is clearly not one that will be read from cover to cover, and in the final analysis its real worth will depend on its suitability as a comprehensive reference source. While preparing this review, I needed to collect a set of literature references for a house staff discussion centered around an infant with the syndrome of iron deficiency with hypoalbuminemia due to gastrointestinal loss of blood and plasma protein. This seemed to be an appropriate test case. How did Hematology of Infancy and Childhood fare? The index contained no mention of this condition, at least not that I could find. A reading of the chapter on iron deficiency did yield an adequate section with several appropriate references on this topic. On the other hand, a more fully detailed and elegantly written discussion of this topic, with ample literature references, could be readily found in Paediatric Hematology (New York, Churchill Livingstone Inc, 1977), a book that I continue to prefer as a first-line resource.

Nathan and Oski's text unquestionably represents the premier compendium on hematologic disease in children, and I recommend it for the libraries of both pediatrics and hematology departments.

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Serum Ionized Calcium Concentrations in Normal Neonates

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 Adult serum ionized calcium (iCa) concentrations are higher when using the newer, highly sensitive, ion-selective electrodes compared with older electrodes. Currently used neonatal normative ranges were established using older electrodes and not under standardized conditions or age. Thirty term infants, carefully screened to exclude confounding factors that could affect serum iCa concentration, were studied at birth and 2 and 24 hours of age for serum iCa concentrations. Mean concentrations declined from 1.45 mmol/L (5.82 mg/dL) at birth to 1.33 mmol/L (5.34 mg/dL) at 2 hours to 1.23 mmol/L (4.92 mg/dL) at 24 hours. The 95% confidence limits at 24 hours ranged from 1.10 to 1.36 mmol/L (4.40 to 5.44 mg/dL). Using newer ionselective electrodes, normal neonatal ranges for iCa concentrations during the first 24 hours of age are higher than published references.

(AJDC 1988;142:516-518)

Tonized calcium (iCa) is the biologically active portion of serum calcium (Ca). The increased availability of newer, more accurate ion-selective electrodes allows the routine use of iCa measurement in clinical care. However, few studies have been undertaken to determine the range of normal for serum iCa concentrations within the first 24 hours of life using these newer electrodes. Comparisons of older electrodes to newer ion-selective electrodes in adults have found the newer ones to be more sensitive. yielding significantly higher values for matched samples. 1,2 We therefore be-

| Time | Mean, mmol/L (mg/dL) | Range, mmol/L (mg/dL) | 95% Confidence Range, mmol/L (mg/dL) |
|----------|-----------------------------------|------------------------------|---|
| Cord | | | |
| Total Ca | 2.6 ± 0.2 | 2.3 – 2.9 | 2.3 – 2.9 |
| | (10.2 ± 0.6) | (9.3 – 11.7) | (9.0 – 11.4) |
| iCa | 1.45 ± 0.08 | 1.32 – 1.64 | 1.30 – 1.60 |
| | (5.82 ± 0.30) | (5.28 – 6.56) | (5.22 – 6.42) |
| 2 h | | | |
| Total Ca | 2.4 ± 0.2 | 2.2 – 2.8 | 2.1 – 2.7 |
| | (9.7 ± 0.6) | (8.8 – 11.3) | (8.5 – 10.9) |
| iCa | 1.33 ± 0.06 | 1.23 – 1.47 | 1.21 - 1.46 |
| | (5.34 ± 0.25) | (4.92 – 5.88) | (4.84 - 5.84) |
| 24 h | THE REPORT OF THE PERSON | | |
| Total Ca | 2.3 ± 0.2 | 1.9 – 2.5 | 1.9 – 2.6 |
| | (9.0 ± 0.6) | (7.8 – 10.0) | (7.8 – 10.2) |
| iCa | 1.23 ± 0.06 (4.92 ± 0.26) | 1.08 – 1.34 (4.32 – 5.36) | 1.10 – 1.36 (4.40 – 5.44) |

lieved that previously published neonates (0.62 to1.25 mmol/L [2.5 to 5.0 mg/dL])3 might not be applicable when using the newer electrodes. Further, past reports measuring iCa concentrations in the normal newborn were either not performed in a select, full-term patient population at precise, standardized, postnatal ages or under standardized clinical conditions specifically excluding factors affecting Ca metabolism. 4-8

In this study, healthy, full-term, vaginally delivered infants had serum total and iCa concentrations measured at birth (cord), 2 hours, and 24 hours of life. The aim of our investigation was to establish, in normal term infants, the mean and range of variation of iCa concentration at 24 hours of life when Ca reaches its physiologic nadir.9 The hypothesis tested was that the more sensitive, newer electrodes would yield iCa concentrations significantly higher than those reported for newborn infants using older electrodes. Further, we hypothesized that,

in normal term infants carefully selected for having no perinatal risk factors that could affect Ca or magnesium metabolism, the serum iCa concentration decreases significantly from birth to 2 and 24 hours of age.

PATIENTS AND METHODS

This study was approved by the Review Board on Investigations Involving Human Beings of the University of Cincinnati Medical Center Hospital. Written informed consent was obtained from the legal guardians of each infant before enrollment in the study. All infants were term (37 to 41 weeks) by dates, confirmed by a physical assessment score within two weeks by the method of Ballard et al,10 modified from Dubowitz's criteria. All children were of appropriate weight for gestational age by the criteria of Usher and McLean.11 The deliveries were vaginal, either spontaneously or by low forceps. Specific exclusions were low Apgar score (<7 at one minute or 8 at five minutes) and any maternal clinical conditions known to affect Ca metabolism such as diabetes, parathyroid, bone, or gastrointestinal diseases.3 No mother received any medications in the perinatal

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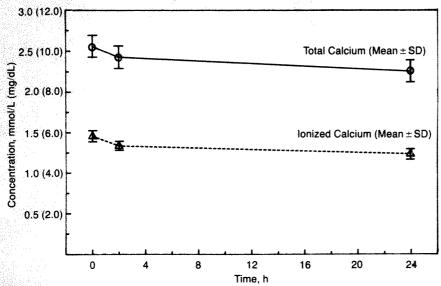


Fig 1.—Relationship of total calcium and ionized calcium concentrations over time. Hour 0 indicates birth.

period that are known to affect either Ca or magnesium metabolism (in particular magnesium sulfate, diuretics, anticoagulants, or anticonvulsants).³

Each child had blood drawn by venipuncture from the placental side of the clamped umbilical vein, then had blood drawn by venipuncture at precisely 2 and 24 hours of life. The blood was immediately placed in a 5% carbon dioxide-containing tube (to stabilize pH) with no anticoagulant. After allowing the blood to clot, the specimen was centrifuged and the serum removed; the portion of serum for iCa was again placed into a 5% carbon dioxide-containing tube and frozen. It has been shown by Moore¹² that freezing has no effect on the concentration of the ionized Ca fraction in serum. None of the infants had been fed by 2 hours of age and all infants had received four to five feedings of human milk (n=1), formula (Similac 20 [Ross Laboratories, Columbus, Ohio]) (n = 27), or a combination of the two (n=2) by 24 hours of life. On a weekly basis, the available frozen serum samples were thawed and assayed on an ion-selective, ionized Ca electrode (Radiometer ICA 1, Radiometer Laboratories, Copenhagen). All samples were pH corrected to 7.40 when necessary. The SE of measurement of this electrode is 0.012 mmol/L (0.05 mg/dL). The total Ca concentrations were also measured on a weekly basis on a spectrophotometer (Varian AA-1475, Varian Instruments, Palo Alto, Calif). The interassay coefficient of variation for Ca is 1.8%.

Data were analyzed using a computerized SAS package. Linear regression was used to analyze the correlation between iCa and total Ca. Repeated measures analysis of variance was used to study variations of

total Ca, iCa, and "bound" Ca over time. Bound Ca is all serum Ca not in the ionized form. This includes protein bound and complexed Ca and is calculated from the following formula: Total Ca - iCa = Bound Ca. Results are expressed as mean \pm SD. A P value of .05 or less was considered significant.

RESULTS

Thirty patients were recruited for the study. Eighteen were male, 12 were female; 20 were black and ten were white. Gestational age was 39.8 ± 1.1 weeks, ranging from 37 to 41 weeks. Birth weight was 3.3 ± 0.4 kg, ranging from 2.6 to 4.1 kg.

Results for total Ca and iCa concentrations are shown in the Table. For both total Ca and iCa the highest serum values were at birth with mean values of 2.6 mmol/L (10.2 mg/dL) and 1.45 mmol/L (5.82 mg/dL), respectively. Each had decreased by 2 hours of age to 2.4 mmol/L (9.7 mg/dL) for total Ca and 1.33 mmol/L (5.34 mg/dL) for iCa (P < .0001). At 24 hours of age, both serum total Ca and iCa concentrations had decreased further (Fig 1. P < .0001) 2.3 ± 0.2 mmol/L $(9.0\pm0.6$ mg/dL), ranging from 1.9 to 2.5 mmol/L (7.8 to 10.0 mg/dL), and $1.23 \pm$ $0.06 \text{ mmol/L} (4.92 \pm 0.26 \text{ mg/dL}),$ ranging from 1.08 to 1.34 mmol/L (4.32 to 5.36 mg/dL), respectively.

At 2 hours of age the decrease in total Ca concentration (0.12 mmol/L [0.5 mg/dL]) was entirely accounted

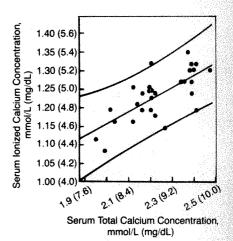


Fig 2.—Correlation of serum total calcium and serum ionized calcium concentrations: regression line and 95% confidence limits of sample of ionized calcium values are shown.

for by the decrease in iCa. While the change from cord blood to 2 hours of age of total Ca and iCa was highly significant (P<.0001), the bound Ca did not change significantly (P=.62). By 24 hours, 75% (0.22 mmol/L [0.9 mg/dL]) of the change in total Ca was due to the fall in the iCa fraction and 25% (0.07 mmol/L [0.3 mg/dL]) was due to a decrease in the bound Ca. The decreases in total Ca, iCa, and bound Ca concentrations between 2 and 24 hours of age were highly significant (P<.001).

Neither the total Ca nor iCa concentrations were affected by the patient's sex, race, or type of milk feeding. There was a significant correlation between serum total Ca and iCa concentrations (r=.71, P<.001, Fig 2).

COMMENT

Dynamic changes in serum Ca concentration occur in the first few days of life, with high cord blood concentrations falling to a nadir at about 24 hours of life and remaining low until 48 to 72 hours of age, before rising again. 4,5,9 The rapidity and depth of fall of the serum total Ca concentration appears to depend on Ca intake, gestational age, and perinatal complications (eg, birth asphyxia, maternal diabetes mellitus).4 The ionized fraction of total Ca appears to behave in a similar manner as the total Ca; however, considerably less information is available because of difficulties in us-

ing the older electrodes. These electrodes required a relatively larger amount of blood, were less sensitive, and were more difficult to maintain in a clinical setting than the equipment available today. Of the available studies on iCa concentrations in the newborn, several used data that were collected over a wide period (three to 48 hours) and then the results were "pooled" to give a mean for the first day, 5,6,8 Because of the known dynamics of total Ca, the timing of blood sampling must be precise and pooling results of samples obtained at varied postnatal ages may be inappropriate if "normal" serum iCa concentrations are to be determined. Other studies have included term and preterm infants to determine a range of normal13; since prematurity is not a normal condition, inclusion of preterm infants theoretically may have altered the reported ranges. Hence, to our knowledge, there are no systematic studies of serum iCa concentrations using the modern ion-selective electrodes, at standardized postnatal ages, in a population of term neonates without any potential perinatal confounding factors. In this study, we have determined that at 24 hours, the normal range (95% confidence limits) for serum iCa was 1.10 to 1.36 mmol/L (4.40 to 5.44 mg/dL). Although the sample size was relatively small (n = 30), the variance and SD were small. Therefore, it is unlikely that a larger sample size would cause any major change in the ranges reported herein. Thus, our results compared with previously published ranges of 0.63 to 1.25 mmol/L (2.5 to 5.0 mg/dL)3 confirm our hypothesis that the use of the modern ion-selective electrodes leads to higher values than previously reported.

To our knowledge, there are no previous studies that have specifically examined the early changes (the first few hours) of serum iCa concentrations. Most authors, using older electrodes, have reported mean iCa concentrations during the first few days of life ranging from 1.07 to 1.17 mmol/L (4.30 to 4.67 mg/dL)^{5.6} and excluded the first hours of life.

In this study, the mean serum iCa concentration of 1.45 mmol/L (5.82 mg/dL)at birth fell to 1.33 mmol/L (5.34 mg/dL) at 2 hours, then to 1.23 mmol/L (4.92 mg/dL) at 24 hours. Thus, the mean serum iCa concentrations are higher than previously reported, decline abruptly from birth to 2 hours, and decline further from 2 to 24 hours of age. More than half of the total decline of the first 24 hours occurs within the first two hours of life (Fig 1). The fall in serum iCa concentration over the first 24 hours of life is the major determinant for the fall in serum total Ca concentration. At 2 hours of age, the fall in iCa concentration accounts for 100% of the decline in total Ca. By 24 hours, the iCa concentration has continued to fall and the bound fraction also has declined but to a lesser degree. Thus, at 24 hours 75% of the decline in serum total Ca concentration is due to a fall in iCa and 25% is due to a fall in the bound Ca fraction.

There is a statistically significant correlation between total Ca and iCa concentrations in serum as shown in this study, but the predictive value of iCa concentration from total Ca concentration is poor (Fig 2). As an example, a total Ca concentration of 2 mmol/L (8 mg/dL) corresponds to a predicted iCa concentration (95% confidence limits) of 1.05 to 1.25 mmol/L (4.2 to 5.0 mg/dL). This range limits the clinical validity of a prediction of iCa concentration from total Ca concentration. This finding confirms other studies that have also shown a high correlation but a poor predictive value for iCa from total Ca concentrations. 5,8,13

CONCLUSION

Despite the fact that the 24-hour values were taken at the period of expected physiologic nadir for iCa concentration, our study shows higher values for neonatal iCa concentrations using the newer ion-selective electrode. In this study the 2 SD range for serum iCa of 1.10 to 1.36 mmol/L (4.40 to 5.44 mg/dL) is much higher than previous "reference ranges" of 0.63 to 1.25 mmol/L (2.5 to 5.0 mg/dL)

that were measured at various postnatal ages, including prenadir, postnadir, and nadir values. As seen herein, serum iCa concentration falls rapidly in the first two hours of life, then falls further to 24 hours of age. The decline in serum iCa concentration accounts for most of the change in total Ca concentration over the first 24 hours of life. Since iCa cannot reliably be predicted from total Ca measurements, we suggest that there is a role for direct iCa measurement in routine clinical care of the neonate.

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Educational Interventions

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Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—Pediatric clerkship programs were evaluated in 1981 and suggestions were made. What has changed since then? This study addresses that question. Will we take our own advice? How should we do it? This article offers positive suggestions and is worth reading.—H.D.A.

A Survey of Undergraduate Pediatric Education

Progress in the 1980s?

Olle Jane Z. Sahler, MD; Jerome P. Lysaught, EdD; Larrie W. Greenberg, MD; Benjamin S. Siegel, MD; Steven E. Caplan, MD; Kathleen G. Nelson, MD

In 1981, Stillman et al¹ published the results of a survey of pediatric clerkship programs in US and Canadian medical schools. The study was prompted by the belief that reorientation of educational goals, redistribution of patients toward outpatient care, and increased numbers of medical students necessitated a reassessment of the structure and function of the categorical clerkship.

Of the 141 pediatric departments contacted by Stillman and coworkers, 119 (84%) responded. How to define objectives for instruction adequately and how to evaluate appropriately students' fund of cognitive information, interviewing and physical examination

skills, and problem-solving ability were the most common and highest-priority concerns of clerkship directors. Frequently identified weaknesses in clerkship design included lack of uniformity in the educational experience, overemphasis on tertiary care coupled with inadequate ambulatory care opportunities, and insufficient student contact with faculty.

When the original study was undertaken, increasing attention was being paid to such issues as teaching by objective and the evaluation of teacher effectiveness.2 Many individuals and groups had begun to construct core curricula. For example, in 1981, the Education Committee of the Ambulatory Pediatric Association (APA) began to systematize a set of competencies and objectives that ideally should be attainable by students during their pediatric clerkship and elective experiences. Core knowledge, skills, and attitudes were identified and suggestions for both the appropriate learning environment and for methods to evaluate student competence were provided for each objective. The final document, Educational Guidelines for Training in General/ Ambulatory Pediatrics (hereafter referred to as the *Guidelines*),³ which represented the consensus of both practitioners and full-time faculty, was published in 1985 and distributed to all APA members.

During 1986, five years after the publication of the article by Stillman et al, we conducted a similar survey to monitor change, if any, in undergraduate education in pediatrics. We also included several questions about the impact, if any, that the distribution of the *Guidelines* might have had on the structure or content of pediatric clerkships to evaluate this particular form of information dissemination.

SUBJECTS AND METHODS

A questionnaire containing items closely matching the 25 items in the original study was mailed to the chairpersons of departments of pediatrics at the 127 medical schools in the United States. A few questions were modified to assess use of resources not in widespread use in 1981 (eg, computer-assisted instruction). Several questions regarding knowledge about and applicability of the *Guidelines* for medical student teaching were added.

The department chairperson was asked to have the director of the third-year pediatric clerkship complete the questionnaire. A follow-up mailing was sent to those

Reprints not available.

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| Table 1.—Organization/Administration of the Clerkship | | | | | |
|---|-----------|-----------|--|--|--|
| 公司的 和中国的东西的东西 | Ye | ear | | | |
| | 1981 | 1986 | | | |
| Required course, % of schools | 94 | 98 | | | |
| Average No. (range) of clerks/rotation | 19 (4-63) | 19 (2-60) | | | |
| Average (range) length of clerkship, wk | 7 (3-16) | 7 (4-10) | | | |
| Directorship, % Chairperson | 18 | 33 | | | |
| Single faculty, not chair | 42 | 40 | | | |
| Committee | 37 | 26 | | | |

| | Schools Reporting, | | Mean % | | Range, % | |
|---------------------------------|-----------------------|------|--------|------|----------|-------|
| Site | 1981 | 1986 | 1981 | 1986 | 1981 | 1986 |
| Outpatient | 77 | 69 | 33 | 32 | 3-75 | 3-100 |
| Inpatient | 78 | 69 | 52 | 55 | 15-99 | 6-95 |
| Well-baby nursery | 55 | 59 | 14 | 8 | 1-40 | 1-33 |
| Intensive care nursery | 27 | 19 | 10 | 8 | 1-25 | 0-30 |
| Other (eg, community rotations) | 20 | 20 | 17 | 20 | 5-35 | 1-17 |

schools failing to respond to the first questionnaire. A total of 98 questionnaires (78%) were completed and returned.

The results are presented as percentages to facilitate comparisons between the data reported in 1981 and those obtained in 1986. It must be noted, however, that because we surveyed medical schools only in the United States rather than in both the United States and Canada, the two studies do not examine precisely the same population. Accordingly, the only comparisons that can be made are those afforded by observing notable similarities or differences and speculating about those findings that appear to be particularly dramatic.

RESULTS

Table 1 is a comparison of the organization and administration of clerkships in 1981 and in 1986. Although there has been a slight increase in the percentage of institutions requiring students to take the pediatric clerkship, the major difference is the shift in administrative responsibility from a committee-type structure to direction by the chairperson.

Table 2 details the composition of the instructional faculty. Whereas the percentage of instruction provided by full-time faculty members and house staff has decreased, the percentage contribution made by associate (clinical) faculty and allied health professionals has increased. As shown in Table 3, the mean percentage of time spent in the ambulatory area and on the inpatient service has remained stable despite the fact that some schools have moved to an exclusively ambulatory-based curriculum, and a considerable body of literature has appeared recently urging major increases in the ambulatory experience for clerks.⁴

Table 4 summarizes how instructional objectives are defined and how factual knowledge is taught and evaluated. There appears to be a continuing trend toward identification of behavioral or competency-based objectives for instruction. The data on evaluation of factual knowledge are more difficult to compare because the second questionnaire was more open ended and offered additional choices. It appears, however, that a number of schools use several types of evaluative tools and that the oral examination is a popular option alone or in combination with another modality. Most striking is the finding that one in five schools do not formally evaluate factual knowledge.

Table 5 compares instruction in and evaluation of interviewing skills between 1981 and 1986. The decline in the percentage of schools with defined performance criteria may be an artifact reflecting the slightly different

Table 2.—Instructional Faculty Year 1981 1986 Full-time faculty 44 37 House staff 39 37 Associate faculty 11 16 Allied health professionals 5 10

| Table 4.—Instruction and Evaluation of Factual Knowledge | | | | | |
|--|------|------|---------------------|--|--|
| | Yea | r, % | 200 | | |
| 127 | 1981 | 1986 | 1 | | |
| Objectives stated (orally or written) | 89 | 96 | | | |
| Definer of factual knowledge objectives Individual subspecialty faculty | 29 | 29 | いまでいる | | |
| Committee | | | | | |
| | 30 | 26 | | | |
| Standard pediatric text | 20 | 26 | | | |
| Evaluator of factual knowledge Short-answer examination | 52 | 56 | | | |
| Old National Board of Medical Examiners–II examination | 33 | 39 | AND REPORTED BY | | |
| Self-instructional units with preclerkship/ postclerkship testing | 10 | 8 | Sales and the sales | | |
| Computer-assisted instruction | 6 | 5 | 1 | | |
| Oral examination* | | 35 | | | |
| Other* | | 24 | | | |
| Not evaluated* | | 20 | | | |

*Not included in Stillman et al.1

populations assessed in the two studies; it seems highly unlikely that a department would discard rather than merely modify performance criteria once they were determined. Instruction is accomplished using a variety of methods. Demonstration and lecture continue to be employed most frequently; the use of assigned reading about how to interview has declined (ie, instructors have less confidence in the efficacy of teaching interviewing using handouts and textbooks) and the use of programmed patients has increased.

Direct observation of an interview continues to be the most popular evaluation tool, although its use has declined somewhat. As was true in

| Table 5.—Instruction and Evaluation of Interviewing Skills Year, % | | | | | | |
|---|------|------|--|--|--|--|
| | Yea | r, % | | | | |
| | 1981 | 1986 | | | | |
| Performance criteria defined | 31 | 20 | | | | |
| How taught Demonstration | 78 | 87 | | | | |
| Lectures | 64 | 61 | | | | |
| Reading assignments | 37 | 10 | | | | |
| Audiovisual replay of faculty with patient | 18 | 15 | | | | |
| Programmed patients* | | 8 | | | | |
| Other* | | 7 | | | | |
| How evaluated Direct observation | 75 | 58 | | | | |
| Audiovisual replay of student with patient | 10 | 11 | | | | |
| Programmed patients | 4 | 8 | | | | |
| Other* | | 13 | | | | |

Not formally evaluated *Not included in Stillman et al.1

1981, interviewing skills are not formally evaluated at one of three schools. This may result from an assumption that interviewing is adequately taught and evaluated during courses in physical diagnosis or that review of written work provides an indirect but adequate measure of the interviewer's skill in eliciting necessary and appropriate information.

33

As shown in Table 6, instruction in physical examination techniques continues to rely heavily on small group demonstration, practice examinations with or without direct faculty observation, and lecture. The use of patients with known findings has increased substantially and videotapes of ideal examinations are used frequently. Faculty observation remains the primary evaluation tool at institutions where formal evaluation is carried out. As was true for the evaluation of interviewing skills, many institutions do not formally evaluate physical examination skills, possibly for the same reasons.

Both instruction in and evaluation of the written record rely heavily on the direct critique of chart notes, a practice reported at 92% of institutions in 1981 and 95% of institutions in 1986.

Instruction in problem solving generally takes place as a group interaction, as shown in Table 7. Evaluation of problem-solving ability has become

Table 6.—Instruction and Evaluation of Physical Examination Skills

| A DESCRIPTION OF THE PROPERTY | Yea | r, % | 7 |
|---|------|------|---|
| | 1981 | 1986 | |
| How taught | | | |
| Small group demonstration | 81 | 78 | |
| Faculty observation of examination | 76 | 77 | |
| Lectures | 61 | 62 | |
| Examination without faculty observation | 61 | 54 | |
| Patients with known findings | 26 | 49 | |
| Videotapes of ideal examinations* | | 31 | |
| Not formally taught | 1 | 4 | |
| How evaluated | | KINK | E |
| Faculty observation | 68 | 67 | |
| Programmed patients* | | 2 | |
| Audiovisual replay of student with patient* | | 7 | |
| Other* | | 17 | |
| Not formally evaluated | 24 | 28 | |

^{*}Not included in Stillman et al.1

less subjective as more objective measures (critique of written work and oral examinations) have been incorporated into the process. The decline in the use of patient management problems may be a reflection of increased use of more interactive tools such as simulated patients and computerbased cases.

Reporting of grades has remained essentially unchanged. The honors/ pass/fail or pass/fail systems continue to be used at slightly more than 50% of schools. Letter grades are given at approximately one third of institutions.

As shown in Table 8, the use of student feedback for the internal evaluation of clerkship program organization and format was universal among programs responding to the 1986 survey; it is also the principal means for evaluating faculty performance. Peer evaluation of teacher effectiveness has not increased, despite evidence that peer evaluation is complementary to student evaluation and is especially helpful in assessing quality, currentness, and appropriateness of content, issues that students may not judge accurately because of limited knowledge of the subject area.5

Identification of major strengths and weaknesses was addressed using

Table 7.—Problem-Solving Ability (Clinical Reasoning)

| | Year, % | |
|---|---------|---------|
| | 1981 | 1986 |
| How taught | | Will Co |
| One-to-one faculty- student interaction* | | 17 |
| Group interaction* | | 74 |
| Application to cases available* | | 9 |
| How evaluated | | REAL |
| Subjective faculty evaluations | 89 | 68 |
| Review of patient write-ups | 50 | 62 |
| Oral problem-solving examination | 36 | 49 |
| Patient management problems | 35 | 26 |
| Simulated patients* | | 26 |
| Computer simulations* | | 3 |
| Not formally evaluated* | | 7 |

^{*}Not included in Stillman et al.1

Table 8.—Internal Evaluation of the Clerkship Program

| AUGUST OF STREET | | | | |
|------------------------------------|---------|------|--|--|
| | Year, % | | | |
| | 1981 | 1986 | | |
| Student evaluation of clerkship | 92 | 100 | | |
| Faculty Student evaluation | 95 | 90 | | |
| Standardized peer evaluation | 7 | 7 | | |
| Not formally evaluated* | | 3 | | |

^{*}Not included in Stillman et al.1

an open-ended question rather than a checklist format. Despite this, the categories identified independently by the respondents in 1986 are remarkably similar to those reported in 1981. As shown in Table 9, interest in teaching, a large and diverse patient population, and good organization continue to rank as major positive attributes of a successful clerkship. Inclusion of ambulatory care in the curriculum is emerging as a fourth major strength.

As is also shown in Table 9, two major weaknesses persist: lack of uniformity in the student experience and high student-to-faculty ratios. Perhaps because of increased awareness about instructional design issues, nonsystematic evaluation processes and poor feedback mechanisms to students about performance ranked as substan-

| Table 9.—Major Program Strengths and Weaknesses | | | | | |
|---|-----------|-------|--|--|--|
| | Year, % | | | | |
| | 1981 1986 | | | | |
| Program strengths | | | | | |
| Faculty/house staff interest in teaching | 55 | 54 | | | |
| Large/varied patient population | 33 | 33 | | | |
| Well-organized clerkship | 12 | 10 | | | |
| Primary care/outpatient experiences* | | 16 | | | |
| Program weaknesses | | V-III | | | |
| Lack of uniformity in student experience | 25 | 18 | | | |
| Insufficient time | 13 | 9 | | | |
| High student-to-faculty ratio | 13 | 19 | | | |
| Overemphasis in tertiary care | 13 | 2 | | | |
| Lack of specific objectives | 8 | 8 | | | |
| Unsystematic evaluation process | 8 | 21 | | | |
| Poor feedback mechanisms* | | 13 | | | |
| Too few subspecialty experiences* | | 7 | | | |
| Lack of financial support* | | 3 | | | |

^{*}Not included in Stillman et al.1

tial weaknesses in 1986. Overemphasis on tertiary care was mentioned less frequently, underscoring the positive impact of including more primary and ambulatory care experiences in the curriculum, as recommended in *Physicians for the 21st Century*. 5

Of the 98 clerkship directors who responded to the questionnaire, only 36 (37%) were familiar with the Guidelines. As indicated in Table 10, the material contained in the document was perceived to be clearly relevant. Most directors felt that changes in the clerkship are or might be needed, however, to incorporate the Guidelines, even though much of the suggested content was apparently already included in the curriculum. From this it might be assumed that the potentially necessary changes would be process oriented with better explication of expectations; development of clearer, more discrete learning objectives; more consistent inclusion of important topics by design rather than by reliance on chance patient availability; and provision of learning modules (computer-assisted instruction, vid-

| | NAME OF STREET | Answer, % | | |
|--|-----------------------|-----------|----|--------|
| | No. of Respondents | Yes | No | Unsure |
| Are you familiar with the Guidelines? | 98 | 37 | 63 | 0 |
| Have you implemented the Guidelines? | 36 | 6 | 94 | 0 |
| Would you participate in a study about implementation? | 36 | 91 | 9 | 0 |
| Material Is relevant | | 91 | 2 | 7 |
| Corresponds with current instruction | | 74 | 11 | 15 |
| Has implications for change | | 46 | 9 | 45 |

eotapes) to supplement didactic and patient-centered teaching. In other words, the scope and content of the objectives in the Guidelines seemed appropriate and reasonable, clerkship directors might be concerned that careful analysis of a given student's experience would be likely to show major deficits in important content areas unless instruction in these topics was actively sought or provided prospectively as part of a planned curriculum. Whereas only two (6%) of the 36 clerkship directors familiar with the Guidelines had attempted implementation on their own, 33 (91%) expressed interest in collaborating on a project to evaluate the effect of implementation on clerkship instruction and student performance.

COMMENT

In 1981, Stillman and coworkers,1 commenting on the results of their survey, suggested that a national network be instituted to promote sharing and standardization of objectives, instructional methods and materials. and evaluation instruments. The authors distributed their findings to all participants within six months of the survey to stimulate (it was hoped) discussion and change. A short time later, the APA began developing, and subsequently published and widely distributed, the Educational Guidelines for Training in General/Ambulatory Pediatrics.3 We have found, however, that five years later little change in clerkship structure and function has occurred. Thus, it appears that neither the publication of survey results nor the nationwide distribution of a set of instructional guidelines are sufficient, in and of themselves, to bring about change. We suggest that what was

lacking in both instances was a planned effort to promote implementation and that the exclusion of this next necessary step has served to impede change in educational process among pediatric clerkships.

During 1987, the education committee of the APA, responding to a preliminary report of our findings, constituted a task force of clerkship directors. The group was charged to identify, develop, distribute, and test instructional materials for a selected subset of the educational objectives defined in the *Guidelines*, and to construct valid and reliable instruments to evaluate student performance for each of these objectives.

The model presented by this task force has potentially far-reaching implications. If, eventually, it were to include all clerkship directors, it could serve as a national forum for dissemination and implementation of innovative instructional materials and methodologies. The concept of such a national organization is not new. For example, a similar association has existed among the 16 pediatric clerkship directors in Canada since 1982. Funding for the organization itself and for collaborative projects is derived from individual departments as well as extramural sources. The association has been successful in developing innovative methods for instruction and evaluation by serving as a forum for the exchange of ideas and for the implementation of change (M. H. Boyle, MD, FRCP(C), oral communication, 1987).

The overwhelmingly positive response of the pediatric clerkship directors to the concept of instituting a formal collaborative network focusing on the development and evaluation of

instructional materials indicates a strong desire for such a formal structure for undergraduate educators in the United States as well. Two factors may be contributing to this perceived need. The first may be a trend toward the assignment of academic pediatricians in their early or middle careers to the position of clerkship director; these individuals need to use student teaching as a research base to achieve promotion and tenure rather than merely assuming this duty as an (academically unrewarding) administrative service to their department.

The second factor may encompass a broader perspective than pediatrics alone. The two studies presented herein, separated by half a decade, illustrate the laboriousness of effecting change in medical education by the customary approach of encouragement, exhortation, and reporting of survey responses. Indeed, the most remarkable feature of these two inquiries lies in the similarity of their findings, even though a national organization such as the APA had, in the interim, developed and distributed a model set of instructional objectives for undergraduate education. Medical educators must realize that planned, organized implementation is essential to effect change in instructional practices and educational outcomes, and they must repond to that realization with appropriate action.

Past practices in undergraduate education reflect the fact that even though clerkship directors are professional educators, most have had little experience with educational methodology. It is time to move forward in systematizing the process of education by such strategies as identification and use of the most efficacious educational interventions, as well as incorporation of technologically sophisticated educational tools into our educational programming. Most importantly, we must recognize that individual clerkship directors, working in isolation, are unlikely to effect even clearly beneficial changes in educational practice on a national scale without the help of a collaborative network. This last point, in particular, is not surprising: collaboration has been the basis for some of the most dramatic and wide-reaching changes in biomedical science in the history of medicine. Is there any reason to believe that those principles of communication and collaboration that we employ in our roles as scientists in the pediatric subspecialties are not equally applicable to our roles as scien-

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6. Physicians for the 21st Century: Report of the Panel on the General Professional Education tists in education?

The singular contribution of the Flexner report⁷ was the broad sweep of its enactment and implementation. Without entering into the argument that organized medicine had largely anticipated and laid the foundation for the recommendations put forth in the report, it is sufficient to recognize that the proposals embodied in that document galvanized medicine in a reformation of education unlike anything before or since. As society, technology, and praxis enter the last decade of the 20th century, it is essential that American medicine and its specialty groups consider carefully the educational issues at hand. Stillman and colleagues1 and current studies all document the continuing need for change in pediatric education. The enduring question is whether we, as physician-educators, will finally take up the agenda that we ourselves have formulated and move on to the implementation, documentation, and evaluation of educational change.8

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We wish to thank Paula Stillman, MD, for graciously providing materials for the development of the questionnaire.

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Naproxen Nephrotoxicity in a 2-Year-Old Child

Patricio E. Ray, MD; Donna Rigolizzo, MD; Diane R. Wara, MD; Carolyn F. Piel, MD

 The development of acute renal failure and interstitial nephritis due to therapeutic doses of nonsteroidal anti-inflammatory drugs has been documented repeatedly in adult patients but is rare in children. We report the occurrence of this complication in a child. Acute renal failure and hyperkalemia developed in a 2-year-old boy with juvenile rheumatoid arthritis after one month of naproxen sodium therapy. The evidence of renal toxic effects became manifest after an episode of dehydration. A percutaneous renal biopsy specimen revealed interstitial nephritis. The patient recovered promptly after withdrawal of the drug.

(AJDC 1988;142:524-525)

A variety of nephrological syndromes have been reported in adult patients receiving therapeutic doses of nonsteroidal anti-inflammatory drugs (NSAIDs). We describe herein the clinical and pathological features of acute interstitial nephritis and renal failure in a 2-year-old boy who received naproxen sodium therapy for one month. We believe that this is the first report of this complication in a patient less than 16 years of age. 2

PATIENT REPORT

A 2-year-old boy with IgA deficiency and systemic juvenile rheumatoid arthritis was referred to the University of California at San Francisco after ten days of intermittent fevers to 40°C, occasional emesis, and marked swelling of his hands and feet. He also had a two-day history of coughing. The patient had been receiving naproxen sodium (20 mg/kg/d) for one month before admission.

On admission, the patient was found to be mildly dehydrated and tachypneic. On physical examination, temperature was 38.5°C; blood pressure, 110/54 mm Hg; heart rate, 133 beats per minute; and res-

Accepted for publication Jan 21, 1988. From the Department of Pediatrics, University of California, San Francisco.

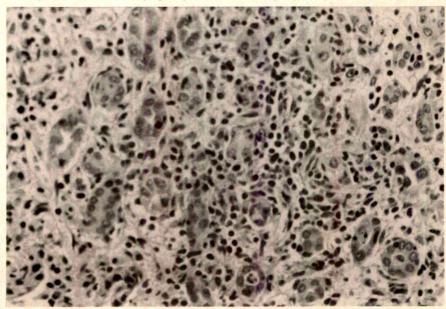
Reprints not available.

pirations, 28/min. Height and weight were both at the 75th percentile. The lungs were clear to auscultation, no adenopathy was present, the spleen tip was palpable 2 cm below the left costal margin, and the liver edge was palpable 3 cm below the right costal margin. Examination revealed increased warmth and minimal effusion of ankles and wrists. Full range of motion was present in all joints. Pitting edema was not present. The patient was estimated to be approximately 7% dehydrated.

Laboratory studies revealed the following values: white blood cell (WBC) count, 15×10^9 /L (15×10^3 /mm³), with 0.22 (22%) band cells, 0.14 (14%) lymphocytes, and 0.64 (64%) polymorphonuclear leukocytes; hemoglobin, 88 g/L (8.8 g/dL); Coombs' test, negative; platelet count, 315×109/L (315×103/mm3); erythrocyte sedimentation rate,75 mm/h; and serum albumin, 20 g/L (2.0 g/dL). Blood urea nitrogen level was 9.3 mmol/L (26 mg/dL), and creatine level was 120 µmol/L (1.3 mg/dL), which were increased from values of 3 mmol/L (8 mg/dL) and 40 µmol/L (0.4 mg/dL), respectively, two days before admission. Urinalysis revealed 0.030 g/d (30 mg/24 h) of protein, 40 WBCs per high-powered field, and a few granular casts. Blood, urine, stool, throat, nasal, bacterial, and viral cultures were negative, as was rheumatoid factor. Neither antinuclear antibody nor antibodies to double-stranded DNA or to extractable nuclear antigen were detected. Serum hemolytic complement C3 and C4 were normal. A right-sided middle lobe infiltrate was suspected on a chest roentgenogram.

The patient was treated with intravenous fluids and cefuroxime sodium (100 mg/kg/d) for five days. Urine output remained good, yet despite adequate hydration, the patient's serum creatinine level continued to rise to a peak of 120 µmol/L (1.4 mg/dL). Repeated urinalyses showed no protein, sediment, or WBCs. A 24-hour urine collection revealed a normal total protein level of 0.15 g/d (145 mg/24h). Renal ultrasound showed enlargement and increased echogenicity of both kidneys but no hydronephrosis, intrarenal mass, or perirenal fluid collections. A percutaneous renal biopsy specimen showed an intense interstitial infiltrate of inflammatory cells consisting predominantly of lymphocytes

Fig 1.—Light micrograph of renal cortical tissue showing interstitial infiltrating lymphocytes, eosinophils, and occasional polymorphonuclear leukocyte (×100).



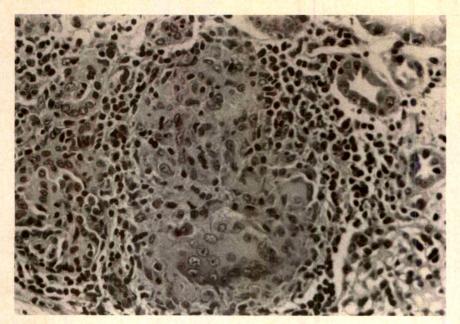


Fig 2.—Light micrograph of renal cortical tissue showing pseudogranuloma (×100).

but also containing numerous eosinophils and scattered polymorphonuclear leukocytes (Fig 1). Diffuse interstitial edema was present. The 20 glomeruli available for evaluation were essentially normal. In some areas, the tubular basement membrane had been completely destroyed, and a pseudogranuloma composed of multinucleated tubular cells mixed with chronic inflammatory cells had formed (Fig 2). Arteries and arterioles were normal. Immunofluorescence microscopy yielded negative findings, with fluorescein-conjugated antisera to IgG, IgM, IgA, C3, fibrinogen,

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2. Cartwright KC, Trotter TL, Cohen ML: Naproxen nephrotoxicity. Ariz Med 1979;36:124albumin, and κ and λ light chains. There was staining with fluorescein-tagged antialbumin antibody of protein absorption droplets in the tubules.

A diagnosis of interstitial nephritis consistent with hypersensitivity to naproxen was made. Naproxen therapy was discontinued on the second day of hospitalization; subsequent daily decreases occurred in the serum creatinine level to 110, 100, and 60 µmol/L (1.2, 1.1, and 0.7 mg/dL). Two weeks after discharge, the serum creatinine level was 40 µmol/L (0.5 mg/dL). During his hospitalization, the patient's

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126.

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serum potassium level rose from 4.2 mmol/L (4.2 mEq/L) to a maximum of 6.7 mmol/L (6.7 mEq/L), requiring treatment with sodium polystyrene sulfonate (Kayexalate). At discharge after seven days of hospitalization, his serum potassium level was 4.8 mmol/L (4.8 mEq/L).

COMMENT

We believe that this patient's acute renal failure, interstitial nephritis, and hyperkalemia are associated with the use of naproxen. Neither biopsy findings nor clinical status suggested acute tubular necrosis. Previous reports concerning adults are in agreement that several factors increase the risk of renal toxicity with NSAID use.3 These predisposing factors occur in clinical settings in which the adrenergic and renin-angiotensin systems are activated in response to low effective circulatory volume, and the renal vasodilatory effect of prostaglandins is necessary to maintain renal blood flow and the glomerular filtration rate.4 With prostaglandin synthesis blocked by naproxen, renal blood flow is not sustained, and hyporeninemic-hypoaldosteronism is induced, with subsequent development of hyperkalemia.5 This case demonstrates that the pediatric population may be at risk for renal toxic effects from NSAID use, especially in the setting of moderate dehydration.

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Quotables:

Writing: Editors are extremely fallible people, all of them. Don't put too much trust in them.

MAX PERKINS, Editor for Hemingway, Fitzgerald, Wolfe, Davenport, and others

Growth Patterns of First-Generation Southeast Asian Infants

Laura-Mae Baldwin, MD, MPH, Shirley Sutherland, MN, ARNP

 The growth patterns of Southeast Asian infants appear to differ from those of the National Center for Health Statistics standards for US children. This study examines the length, weight, and head circumference curves of 175 healthy, full-term, US-born Laotian and Cambodian infants seen periodically at a pediatric clinic from birth to 18 months of age. The median length, weight, and head circumference values of these infants were significantly lower than those of the National Center for Health Statistics standards for infants older than 6 months. These differences were more striking in girls than boys. A decision to observe rather than to pursue a diagnostic work-up in an otherwise healthy Southeast Asian infant who exhibits a slow growth pattern may be the most appropriate management style.

(AJDC 1988;142:526-531)

With the resettlement of refugees in the past ten years, increased numbers of Southeast Asian infants and children have entered the US health care system. Providing basic wellchild care to this group has proven to be a challenge to health care workers as we try to evaluate their growth based on standards developed by the National Center for Health Statistics (NCHS). The NCHS growth standards for children from birth to 36 months of age were developed from data collected from 827 children who were followed up longitudinally between 1929 and 1975 by the Fels Research Institute, Yellow Springs, Ohio.1 The population represented by the NCHS growth curves differs ethnically, environmentally, and temporally from Southeast Asian infants seen in clinicians' offices today, raising questions about the use of these curves for this group.

In the course of our clinical practices, we observed that healthy, US-born Southeast Asian infants' growth dropped more frequently than that of children of other ethnic groups toward the fifth percentile of the growth curves developed by NCHS. Failing growth without recovery dictates a period of frequent observations and often a formal evaluation investigating one or more of the causes of failure to thrive. High rates of anemia, parasitic infections, tuberculosis, and other infectious diseases are well-known problems of the Asian refugees.^{2,3} Therefore, clinicians must consider failure to thrive as a cause of growth failure in Southeast Asian children. On the other hand, given the small size of Southeast Asian adults, could the infants' slowed growth represent this group's normal pattern?

Eveleth and Tanner's review4 of the world literature supports the commonly held belief that the growth patterns of infants and children throughout Asia differ from those of other populations. However, no studies have examined the growth of Southeast Asian refugee children born in the United States. To help the clinician better manage the wellchild care of Southeast Asian infants. this study characterizes the growth of a group of healthy. US-born Southeast Asian infants with no evidence of failure to thrive in the first 18 months of life. It examines their growth patterns for similarities to and differences from the NCHS standards.

SETTING

Approximately 808811 Southeast Asian refugees, primarily Laotian, Vietnamese, and Cambodian, have immigrated to the United States since 1975.5 The Southeast Asian refugee population in the state of Washington numbers 39 200, ranking third behind California and Texas. Approximately 60% of this group lives in King County (oral communication, J. Riess, MCP, 1988). The infants included in this study were patients from the Children's Clinic at Harborview Medical Center, Seattle, a member of the University of Washington hospital system. Harborview Medical Center provides inpatient and ambulatory care to a multiethnic population in inner-city Seattle, as well as to numerous special groups throughout King County, including Southeast Asian refugees. The Children's Clinic, with an average of 600 visits per month, provides ambulatory care to this same urban, lowincome, multiethnic population. Approximately 25% of the clinic visits are made by Southeast Asian infants and children. Laotian and Cambodian translators were available half-time in the Children's Clinic for the first year of the study and full-time for the remaining period.

SUBJECTS AND METHODS

We identified all Southeast Asian infants who were born between May 1980 and September 1984 and who had been seen in the Children's Clinic between birth and 18 months of age. Through chart review, we excluded the following infants from the study: (1) those born outside the United States; (2) those born before 37 weeks' gestation; and (3) those born with complications at birth or who had chronic illness in infancy. Two hundred seven infants qualified for the study. We extracted the following information from the charts of these infants: ethnic group, sex, date of birth, and hospital of birth. Weeks of age, weight in kilograms, and recumbent length and head circumference in centimeters were re-

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University of Washington School of Medicine,
Seattle (Dr Baldwin), and Department of Pediatrics, Harborview Medical Center, Seattle (Ms

| Table 1.—Ethnicity of Original Sample | | | | |
|---------------------------------------|------------|--|--|--|
| | No. (%) of | | | |
| Laotian | 101 (48.8) | | | |
| Cambodian | 74 (35.7) | | | |
| Vietnamese | 25 (12.1) | | | |
| Mixed ethnic | 7 (3.4) | | | |
| Total | 207 | | | |

corded from each well-child visit not complicated by illness and from minor-illness visits, such as follow-up for otitis media or dermatitis.

Weight, length, and head circumference measurements were performed by regular clinic staff. Infants were undressed before measurement. Weights were recorded in kilograms to the nearest 0.01 kg. A springtype scale was used to measure all weights until January 1984, after which a digital electronic scale was used. Staff used a right-angle measuring device to obtain crown-to-heel length measurements of infants in the recumbent position with both legs extended and feet at right angles. Lengths were recorded to the nearest 0.1 cm. Brow-to-occiput head circumference was measured to the nearest 0.1 cm using an insertion-type plastic measuring tape.

Several features of this data set complicate its analysis. First, we exerted no control over the frequency and ages at which infants were brought to the clinic for care. Each infant had a variable number of total visits, and there was little uniformity to the weeks of age at which the infants were brought to the clinic. Second, each infant contributed more than one growth point to the data set, a characteristic of longitudinal data collection. Third, there was an increasing amount of variation in growth measurements from birth through 18 months of age. The latter two features of the data set, dependency of growth points and heteroscedasticity of the data, represent violations of the assumptions needed to use linear regression, a tempting analytic technique. To solve these problems, we created a unique method of analy-

First, we defined two study samples. The "total sample" included the original 207 infants who qualified for the study. We also defined a smaller "subsample" of infants. Infants who qualified for the subsample each had at least six growth points that were evenly spaced over the first 18 months of life. Infants with less than six evenly spaced growth points were excluded from the subsample.

We used polynomial regression techniques on the growth points of the total sample to define the best-fitting regression

| | | Journal Office | eria for Inclus | norr iii oubi | sample | |
|-----------------------|--------------|----------------|-----------------|---------------|---------|---------|
| | The Party of | | No. (%) o | f Infants | | |
| | | M | | | F | |
| | W | L | НС | W | L | нс |
| Included in subsample | 41 (44) | 34 (37) | 33 (35.5) | 45 (55) | 42 (51) | 41 (50) |
| Excluded | 52 (56) | 59 (63) | 60 (64.5) | 37 (45) | 40 (49) | 41 (50) |
| Total | 93 | 93 | 93 | 82 | 82 | 82 |

*W indicates weight; L, length; and HC, head circumference.

functions for weight, length, and head circumference for the group. We applied these same functions to each member of the subsample to predict weight, length, and head circumference values for individual infants at each of seven ages: birth and 1, 3, 6, 9, 12, and 18 months. We then calculated the median, or 50th percentile, of the predicted growth parameters for this subsample of infants at each of these ages. We compared the 50th percentile values of our sample with NCHS standards both visually, after plotting them onto NCHS curves, and statistically, with the sign test. Weight-forlength figures, which are independent of age and less dependent on ethnicity, were also plotted onto NCHS curves.

We created a second analytic method to check the accuracy of our first regression technique. We grouped the data from the total sample into several "windows of time," advanced the window by one week, and calculated the median growth point for each window of time. For example, we aggregated all growth points recorded on infants between birth and 3 weeks of age and then calculated the median for the points in this window of time. We repeated this process for all points between 1 and 4 weeks, 2 and 5 weeks, and so forth. We plotted the medians from each window of time onto the curves drawn with the regression techniques to compare the results of the two methods. The advantage of this second technique is its use of the total sample of growth points rather than the smaller subsample.

RESULTS

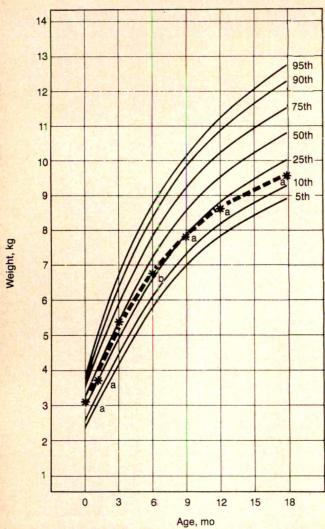
Table 1 shows that 84% of the infants eligible for the study were Laotian and Cambodian. Because of their small numbers, we excluded infants of Vietnamese and mixed ethnic origin, leaving 101 Laotian and 74 Cambodian infants in the total sample. Forty-seven percent of these infants were female and 53% were male. Ninety-five percent of the infants were born at the University Hospital, Seattle.

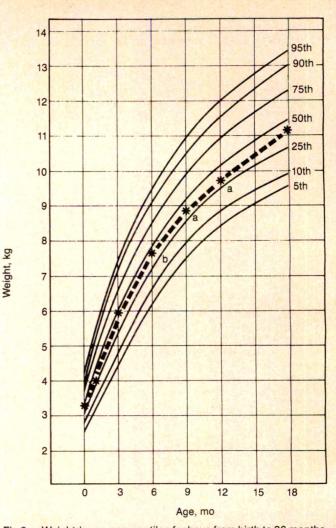
Each infant had between two and 15

measurements, with an average of 7.4 measurements. We recorded values for 1286 weight, 1134 length, and 1087 head circumference measurements for these 175 infants. Ninety-seven percent of the infants began care at the Children's Clinic within the first two months of life. Ninety-four percent of infants were bottle-fed from birth. An equal number participated in the Special Supplemental Food Program for Women, Infants, and Children (WIC).

We defined regression functions that modeled sex, weeks of age, and various polynomials of weeks as the independent variables and weight, length, and head circumference as the dependent variables. The following regression equations were fitted: (1) weight is equal to $A + B (\ln weeks)^2$; (2) length is equal to A+B (ln weeks)2; and (3) head circumference is equal to $A + B \text{ (weeks)} + C \text{ (ln weeks)}^2$, in which A indicates the intercept of the curve; B and C, unstandardized regression coefficients that determine the slope; and ln weeks, natural logarithm of weeks. Each of these regression models explained over 90% of the variance in weight, length, and head circumference. Male and female infants were found to have noncoincident growth curves and were thus examined separately.

Table 2 shows the number of infants who qualified for inclusion in the smaller subsample with six or more evenly spaced weight, length, and head circumference measurements in the first 18 months of life. Over 50% of infants were excluded from the regression analysis because they did not meet these criteria. The infants included in the analysis had an average of nine recorded measurements, while the excluded infants had an average of seven measurements. The previously





Age, mo Fig 2.—Weight-by-age percentiles for boys from birth to 36 months of age. a indicates P<.001; b, P<.05.

Fig 1.—Weight-by-age percentiles for girls from birth to 36 months of age. a indicates P<.001; b, P<.05.

defined regression equations were fit to each individual in the subsample. We extrapolated weight, length, and head circumference measurements at birth and 1, 3, 6, 9, 12, and 18 months of age from each infant's predicted curve, then calculated the median at each of these ages.

Figures 1 through 6 superimpose the subsample's medians for length, weight, and head circumference onto the NCHS growth curves. The median weights of both male and female infants roughly coincided with those of the NCHS curves until 6 months of age, when the curves of the female infants dropped below the NCHS median curve. At 9 months of age, the median weights for both sexes had clearly fallen below the NCHS median. By 18 months of age, the median

weight for female infants was below the NCHS 25th percentile. The fall in median weight for male infants was less striking but still significantly lower than the NCHS 50th percentile.

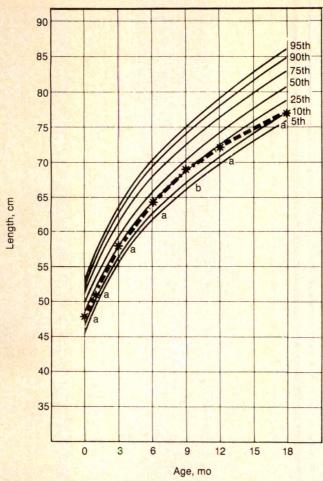
Length and head circumference measurements show similar patterns. However, both male and female infants exhibited significantly lower median lengths than the NCHS medians either at birth or within the first month of life. This lower median length persisted for both groups to 18 months of age.

Weight-for-length measurements in the two sexes are shown in Figs 7 and 8. In both groups, each median weight for length was above the 50th percentile until the infants reached a length value that would correspond to that of a 6-month-old infant. At this point the weight-for-length median drops to the 50th percentile for male infants and below the 50th percentile for female infants.

Although the results are not shown herein, our windows-of-time technique, which uses the total sample, corroborated the findings of the regression method. The medians generated by the grouped data technique were comparable with those generated by the regression method that uses the smaller subsample.

COMMENT

In 1980 the Centers for Disease Control (CDC), Atlanta, first reported data on Southeast Asian infants' growth from a subsample of their study of 400 000 screening visits for



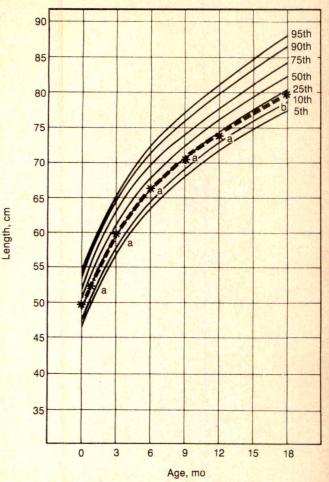


Fig 3.—Length-by-age percentiles for girls from birth to 36 months of age. a indicates P<.001; b, P<.05.

Fig 4.—Length-by-age percentiles for boys from birth to 36 months of age. a indicates P < .001; b, P < .05.

the WIC and the Early and Periodic Screening, Diagnosis, and Treatment Program.³ The CDC reported that up to 25% of Southeast Asian infants less than 12 months old had lengths below the fifth percentile on the NCHS growth charts. In 1981, Peck et al6 reported similar findings in a sample of 821 Southeast Asian infants from four clinics serving large numbers of refugees in the states of California and Washington. They found that 31% to 33% of Southeast Asian infants between birth and 23 months of age had heights for age more than 2 SDs below the NCHS mean, and 14% to 18% of the same infants had weights for age more than 2 SDs below the NCHS mean. In 1984, Olness et al7 compared the anthropometric measurements of 1650 Southeast Asian children in refugee camps and the surrounding Thai villages with the NCHS standards. Between 40% and 55% of these children

aged 9 months to 13 years had weight and height measurements for age that were more than 2 SDs below the NCHS mean.

The degree to which the growth of the children in these three studies fell below the NCHS standards is striking. However, each of the studies included children who had spent some or all of their lives in Southeast Asia, where poor nutritional or socioeconomic conditions may have played an important role in determining their growth patterns.

Using two separate analytic methods, we have confirmed our clinical observation that the growth pattern of US-born Southeast Asian infants differs from the pattern of the standard NCHS growth curves. Since over 50% of the infants were excluded from the regression analysis because of insufficient numbers of growth points, the corroboration of our windows-of-time

technique was crucial. If the smallest infants who required frequent observation made up the majority of the subsample, our findings from the regression technique could represent an underestimate of the normal growth of Southeast Asian infants. However, the second analytic technique using the total sample showed comparable medians throughout, making this scenario an unlikely one.

We do not presume to have elucidated a clear-cut cause for this growth pattern difference. Attempts to separate the genetic and environmental determinants of growth have surfaced frequently, but investigators have never drawn indisputable conclusions. However, the inclusion criteria for this study diminish the effects of several environmental factors on the growth of these infants. First, the inclusion of only full-term infants without identified chronic disease or birth

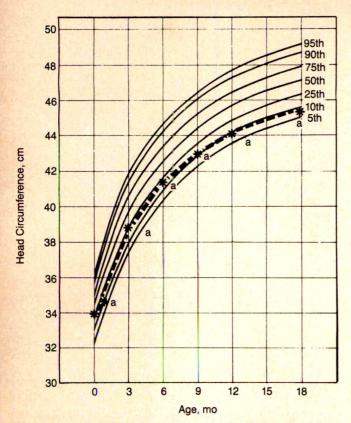


Fig 5.—Head circumference-by-age percentiles for girls from birth to 36 months of age. a indicates P<.001; b, P<.05.

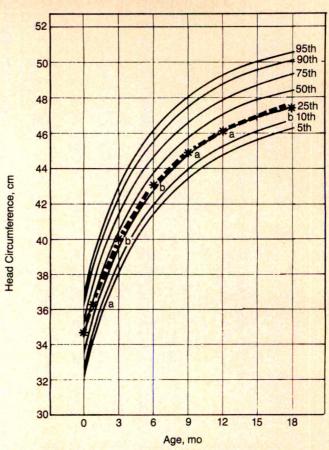


Fig 6.—Head circumference—by-age percentiles for boys from birth to 36 months of age. a indicates P<.001; b, P<.05.

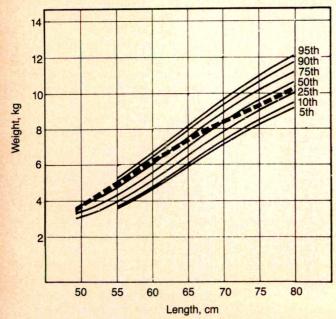


Fig 7.—Weight-by-length percentiles for girls from birth to 36 months of age.

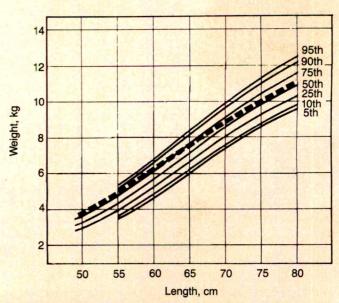


Fig 8.—Weight-by-length percentiles for boys from birth to 36 months of age.

complications helped ensure that infants with conditions that can compromise growth were excluded from the study population. Second, 94% of the infants were being bottle-fed and receiving food vouchers through the WIC program, ensuring the availability of adequate nutrition. Although WIC nutritionists at the Harborview Children's Clinic reported variable success in introducing solids to these infants at 6 months of age, infants receiving an adequate volume of properly prepared formula should not require solid foods for normal growth until approximately age 1 year (oral communication, P. Pipes, MPH, RD, 1986). Therefore, nutritional deficiency intervening at 6 months of age is an unlikely cause of the slowed growth pattern.

Work performed in other Asian countries corroborates the findings of this study. Eveleth and Tanner's review of the literature examining Asian populations' growth between birth and 1 year of age reveals that with only one exception these groups have mean weights within the European range until 6 months of age, when they begin to "fall off" the curve. Growth curves developed for Thai infants, then superimposed on NCHS curves, show a similar phenomenon." Thai infants follow NCHS standards until about 6 months of age, when their median curve falls to about the NCHS 25th percentile for both male and female infants. The nutritional, medical, and socioeconomic differences between Asian infants born in the United States and those born in Asia are formidable, however, and make direct

comparisons between these studies and our results questionable.

Barr and colleagues' study¹² of the growth patterns of Asian children and

Barr and colleagues' study12 of the growth patterns of Asian children enrolled in San Francisco's Kaiser Pediatric Multiphasic Program provides important data on an Asian population living in the United States. Children enrolled in this program came from families where at least one parent was working and receiving health insurance, thereby loosely controlling for medical, nutritional, and socioeconomic status. Although infants younger than 1 year were not included in this study, children 1 year of age and older were generally shorter and lighter than their NCHS counterparts until the age of 14 years, when boys caught up to the NCHS standards but girls continued to lag behind. At least until the age of 14 years, Asian children in the United States have also shown differences in their growth patterns when compared with NCHS standards.

This work is limited by the selected nature of the clinic's urban, low-income patient population. We were unable to adjust for socioeconomic status in the analysis, leaving open the question of its influence on our study results. Low socioeconomic status might affect infant growth through (1) an inability to provide adequate nutrition or (2) psychosocial stress in the home, which is one cause of failure to thrive. The participation of nearly 100% of infants in the WIC program ameliorates the first mechanism. Psychosocial stress is difficult to measure, however, and its effect on these families is unknown. Examining the growth patterns of a

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control group of non-Southeast Asian infants from our clinic might help clarify this issue, but for logistic reasons this examination was not done. With these limitations in mind, the features of this infant population must be carefully reviewed when generalizing the results of this work.

IMPLICATIONS

Physicians are currently using their best clinical judgment to manage the care of Southeast Asian infants whose growth patterns differ from those published by the NCHS. Often, this involves an observational period rather than aggressive diagnostic measures in an otherwise normal infant. The findings of this work can help reassure clinicians choosing this observational path that a slowed growth pattern appears characteristic of healthy, fullterm, US-born Laotian and Cambodian infants with sound nutritional supplementation and counseling of their parents. However, the relatively small number of infants used in this analysis and our inability to clearly separate the effects of genetic and environmental factors on growth preclude the substitution of these curves for the NCHS standards.

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This work was completed while Dr Baldwin was a Robert Wood Johnson Clinical Scholar. The opinions, conclusions, and proposals in the text are those of the authors and do not necessarily represent the views of the Robert Wood Johnson Foundation.

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Necrotizing Enterocolitis in Full-term Infants

A Case-Control Study

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 We performed a case-control investigation of 43 full-term infants with necrotizing enterocolitis (NEC) to identify possible risk factors and unique features of the disorder in the more mature Infant. Two control groups were used. The first consisted of "healthy" term infants. The second was a group of "sick" term infants who did not develop NEC. The 43 term infants with NEC represented 12.7% of all 338 neonates with NEC. The median age at onset of symptoms was 2 days, and 18 infants developed NEC on the first day of life. Two (4.7%) of the 43 affected term infants dled, while 35 (11.9%) of 295 preterm infants with the disorder died. Only three of the full-term infants who subsequently developed NEC had entirely unremarkable courses prior to the onset of symptoms. Sick infants, in particular those who are small for gestational age or require exchange transfusions, are at risk for NEC. Several other features that may be associated with the subsequent development of NEC include the following: perinatal asphyxia, presence of umbilical catheters, antecedent respiratory distress, polycythemia, and maternal preeclampsia. Full-term infants with these features should be treated with cautious observation and aggressive management early in the neonatal period should they develop signs and symptoms suggestive of NEC.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the US Air Force, or the Department of Defense.

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N ecrotizing enterocolitis (NEC) is the most common gastrointestinal emergency presenting during the neonatal period.1.2 The onset of NEC typically occurs at 3 to 10 days of age. albeit up to 31% of the cases may occur after 2 weeks of age.3-5 Although NEC is commonly thought of as occurring almost exclusively in premature infants, it is estimated that 5% to 25% of cases occur in infants of greater than 38 weeks' gestation.3,6 Of the many reviews of the disorder, however, the largest population of term gestation infants consists of only 13 affected children.3,4-9 In addition, controlled investigations have demonstrated that there are no consistent risk factors among infants with NEC compared with matched infants without the disorder.1,5 One must note, however, that these previous controlled studies have included all infants with NEC, the majority of whom were premature. We conducted a case-control study of NEC in 43 full-term infants to identify possible risk factors and unique features of the disorder in newborns of greater maturity.

PATIENTS AND METHODS

We examined the records of all infants with NEC who had been born in US Army hospitals, worldwide, during the period from Jan 1, 1980, through Dec 31, 1985. This information was obtained through the US Army Patient Administration and Biostatistics Activity at Fort Sam Houston, Tex. The initial data consisted of the dates of hospitalization, gestational ages of affected infants, and all diagnoses made. Once infants of term gestation were identified, the individual hospitals were contacted and the actual inpatient hospital records were obtained and reviewed.

We defined a case of NEC as an illness in an infant fulfilling the modified staging criteria of Bell et al¹⁰ for definite or advanced NEC.2 As such, affected infants had clinical signs and symptoms of NEC, as well as definitive roentgenographic and/ or pathologic findings. For each case of NEC two case-control infants were chosen. The first was a randomly selected term gestation infant born at the same US Army hospital within 24 hours of the affected child. The second control subject was the first full-term neonate who was considered to be "sick" born in the same facility subsequent to the affected child. These were infants who had been indexed as having been "seriously ill" or "very seriously ill." The records of the control infants were similarly obtained and reviewed. Gestational ages for all newborns were determined from the maternal menstrual history and confirmed by physical and neurologic findings.11 Small-for-gestational-age and large-for-gestational-age infants were defined by birth weights of less than the tenth or greater than the 90th percentile for gestational age, respectively.12

Data were evaluated for significance using χ^2 analysis, the two-tailed Fisher's exact probability test, and Student's t test. The multivariate analysis method of Holford et all³ was used to assess the effect of multiple variables. This is a linear logistic model in which we evaluated the individual effects of the discrete variables listed in the Table. In this manner we were able to distinguish which potential risk factors were independently most closely associated with the outcome (NEC).

RESULTS

During the six-year period of the investigation, 264789 infants were born in Army hospitals. Three hundred thirty-eight of these neonates were subsequently diagnosed as having NEC. Forty-three (12.7%) of the affected newborns were of 38 weeks' or greater gestation and were considered to be "full term." The overall occurrence of NEC was 1.3 cases per 1000 live births. Of the 247339 full-

Selected Features in 43 Term Infants With Necrotizing Enterocolitis (NEC) Compared With Case-Control Infants*

| Feature | infants With NEC, No. (%) | "Healthy" Control Infants, No. (%) | "Sick" Control Infants, No. (%) | | |
|--|---------------------------------|--|---------------------------------------|--|--|
| Mean birth weight, g | 3203 | 3315 | 3151 | | |
| Mean gestational age, wk | 39.9 | 39.9 | 39.8 | | |
| Perinatal asphyxia | 18 (41.9) | 2 (4.7)†‡ | 11 (25.6) | | |
| Umbilical catheter | 16 (37.2) | 0† | 15 (34.5) | | |
| Respiratory distress | 13 (30.2) | 1 (2.3)† | 20 (46.5) | | |
| Small for gestational age | 11 (25.6) | 1 (2.3)†‡ | 3 (7.0)‡§ | | |
| Large for gestational age | 9 (20.9) | 5 (11.6) | 6 (14.0) | | |
| Hypoglycemia (serum glucose <1.7 mmol/L [<30 mg/dL]) | 9 (20.9) | 5 (11.6) | 3 (7.0) | | |
| Exchange transfusion | 9 (20.9) | 0† | 2 (4.7)§ | | |
| Maternal preeclampsia | 8 (18.6) | 1 (2.3)†‡ | 4 (9.3) | | |
| Polycythemia (hematocrit >0.65 [>65%]) | 7 (16.3) | 0 † | 3 (7.0) | | |
| Myelomeningocele | 3 (7.0) | 0 | 0 | | |
| Death | 2 (4.7) | 0 | 4 (9.3) | | |

^{*}Differences are not statistically significant unless otherwise noted.

term infants born, 5491 had been considered to be sick. The frequency of the disorder among all term infants was 0.17 per 1000 live births, while among premature infants it was 16.9 per 1000 live births. These figures probably underestimate the occurrence of NEC among "Army-born" neonates. In several of the smaller military hospitals, infants who are more than moderately ill are transferred to the nearest civilian level 3 nursery rather than to more distant government centers. In addition, there may have been records in which the diagnosis of NEC was inadvertently not indexed.

There was no seasonal variation of the disorder. We defined an epidemic as four or more episodes of NEC during any three consecutive months in each particular facility. Sixteen (37.2%) of the 43 affected term infants had their conditions diagnosed during such epidemics at their particular institution. Of the 295 identified premature infants with NEC, 118 (40.0%) had their conditions similarly diagnosed during an apparent outbreak. Two (4.7%) of the 43 affected term

infants died. However, only one of the deaths could be directly attributed to NEC. In contrast, 35 (11.9% [P < .001]) of 295 preterm infants with the disorder died. One of the 41 survivors had recurrence of NEC. Eighteen (41.9%) of the 43 full-term children had the initial clinical manifestations of NEC on the first day of life (17 had been fed). The median age of onset of the disorder was 2 days of age. Two infants had incipience of symptoms at 17 and 48 days, respectively. These were both chronically ill, neurologically impaired children who required mechanical ventilation and had repeated episodes of hypoxemia. Excluding these two infants, the mean age of onset of symptoms was 1.6 days. A total of six (14.0%) of the 43 infants with NEC had not been fed prior to the onset of their clinical symptoms. Selected characteristics of the study infants compared with their matched control subjects are presented in the Table. When compared with the healthy control subjects, significant features (P < .01) in the affected neonates included perinatal asphyxia, the presence of an umbilical catheter, respiratory distress, smallness for gestational age, exchange transfusions, maternal preeclampsia, and polycythemia.

When compared with the sick control infants, the affected group had significantly higher frequencies (P<.05) of exchange transfusions and smallness for gestational age. Although not statistically significant, three of the infants with NEC had myelomeningoceles and nine had histories of preceding hypoglycemia. Only three of the children with NEC had been term, healthy, appropriate for gestational age, and had had apparently unremarkable prenatal and postnatal courses prior to the onset of clinical symptoms. When compared with the "well" control infants, asphyxia, smallness for gestational age, and maternal preeclampsia were demonstrated to be independent variables associated with NEC. When compared with the sick control infants, the sole independent risk factor was smallness for gestational age.

COMMENT

Since its recognition as the preeminent serious gastrointestinal tract disorder encountered in the newborn, NEC has typically been thought of as a disease exclusively affecting premature infants.1,2,6 Several epidemiologic perspectives have noted, howfull-term ever. that neonates constitute 5% to 25% of the cases of NEC.1,3,4,6 The current investigation represents the largest reported group of term infants with the disorder. We found that 43 (12.7%) of 338 affected infants are of 38 weeks' or greater gestation, confirming the previous reports.

The most important risk factor for NEC is prematurity. We found a 100-fold increased risk for the disorder among premature compared with all full-term infants. The few published controlled investigations have demonstrated no other consistent risk factors among infants with NEC compared with unaffected matched newborns. 1.5.14 The majority of infants in these particular studies were of premature gestation. As such, both control and affected infants were quite likely to have possible risk factors

[†]Significant at P<.01.

[‡]Significant independent risk factor as determined by the method of Holford et al.¹³

[§]Significant at P<.05.

Seven partial and two double-volume exchange transfusions.

(respiratory distress, umbilical catheters, asphyxia, etc). Due to this lack of distinct elements of susceptibility, Kanto et al¹⁵ hypothesized that the development of NEC is primarily due to immaturity of the gastrointestinal tract rather than to ischemia. This group found that maternal toxemia was inversely related to the presence of NEC in premature newborns. In contrast, we have found a significant association of maternal preeclampsia in full-term infants who subsequently develop the disorder.

Wilson et al7 reported the cases of a group of infants with birth weights of more than 2000 g with NEC in whom significant risk factors included a hematocrit of more than 0.6 (>60%), hypoglycemia, and respiratory distress. In a noncontrolled report of 13 term infants with NEC, five affected children had congenital heart disease while the remaining eight developed the disorder after the 25th day of life following protracted diarrhea.6 In addition, de Gamarra et als reported an epidemic of NEC in 12 infants with a gestational age of 38 weeks or greater in whom a corona virus outbreak was implicated as contributing to the disorder. Kliegman and Fanaroff reviewed the features of NEC in 123 neonates. Of the nine full-term infants with the malady, four were polycythemic, two had cyanotic congenital heart disease, and one had been asphyxiated. The current investigation appears to identify several features that may place full-term infants at risk for NEC: perinatal asphyxia, polycythemia, respiratory distress, history of partial or double-volume exchange transfusions, presence of umbilical catheters, smallness for gestational age, maternal preeclampsia, and, perhaps, the presence of hypoglycemia or a myelomeningocele. Several of these factors are interrelated: polycythemia, umbilical catheters, and exchange transfusions, as well as respiand ratory distress umbilical catheters. Two previously identified determinants, congenital heart disease and protracted diarrhea, were not confirmed by this investigation. Simply speaking, sick term infants are more likely to get NEC than healthy newborns. The majority of term gestation neonates who ultimately develop NEC will exhibit some feature that should make them stand out as being at increased risk for the disorder. These specific perinatal factors would generally appear to affect gastrointestinal tract blood flow or might result in gastrointestinal tract ischemia. Thus, in full-term infants the aspect of relative gut immaturity may play a lesser role in the pathogenesis of NEC.

Black et al16 recently suggested that the type of solution used for partial exchange transfusions (specifically, fresh frozen plasma) may be responsible for the extraordinarily high incidence of NEC in their series of patients with polycythemia. This investigation does not corroborate their belief. In the nine infants we have described, NEC appeared following the use of a variety of exchange solutions (5% albumin, human plasma protein fraction [Plasmanate], "diluted" Ringer's lactate, and fresh frozen plasma). Black and associates found that 81% of "exchanged" hyperviscous infants had some type of gastrointestinal tract problem (19% NEC), compared with 58% of "nonexchanged" hyperviscous infants (0% NEC). Possible mechanisms could include improper catheter placement, thromboembolic phenomena, or relative ischemia from the "thick blood" failing to deliver oxygen. This high degree of association between polycythemia and NEC has not been our experience.17,18 In a previous investigation, we found that fewer than 2% of 932 polycythemic infants subsequently developed NEC.18

Necrotizing enterocolitis following exchange transfusion is believed to have low morbidity and mortality.1 Our findings generally support this belief. Eight of the nine affected infants who had had either partial or double-volume exchange transfusions had relatively uncomplicated hospital courses. However, one of the infants who required a partial exchange transfusion for polycythemia (performed via peripheral catheters with human plasma protein fraction) had a subsequent course complicated by NEC, Escherichia coli, and then Bacteroides fragilis septicemia, disseminated intravascular coagulation, seizures, and multiple perforations of the intestine that required four separate laparotomies.

The typical onset of NEC is between the third and tenth days of life. ^{1,2} Thilo et al² found that 16% of 79 infants with NEC had the onset of clinical symptoms on the first day of life. These infants were larger and more mature than those with later onset. In addition, although few full-term neonates were affected, both Stoll et al⁵ and Teasdale et al¹⁹ have noted an inverse relationship between gestational age and age at onset of NEC. We have confirmed that larger, more mature infants are more likely to develop the disorder early in the neonatal period.

A significant percentage of the cases of NEC (37.2% in full-term and 40.0% in premature infants) occurred during "epidemics" in specific hospitals. This finding lends further credence to the hypothesis that NEC, in part, is an infectious disease. 1.2.4.8 We were unable to identify specific pathogens that could be implicated at particular institutions.

Twenty-one percent (9/23) of the term infants in the current investigation required surgical intervention. This contrasts with the 35% to 68% frequency of surgery noted in previous reports. 5,7,9,20,21 These earlier accounts were from an era in which early manifestations of NEC may not have been as aggressively treated as they currently are. Furthermore, "classic" NEC has a reported mortality of 20% to 56%.1,4,5,7,9,20,21 We found a mortality rate of only 4.7% (2/43) among term infants and 11.9% (35/295) among premature infants with NEC. These findings may reflect a less severe form of the disorder among term infants, as well as improved diagnosis and management of the entity among all infants.

Reports of a mild form of NEC termed "benign pneumatosis coli," 1,22 have appeared. This condition is said to occur in more mature infants who present with frank hematochezia. Affected children are minimally symptomatic and have abdominal roentgenograms characterized by the presence of isolated sigmoid or colonic pneumatosis. None of the 43 infants we

describe would appear to fit this classification. The affected infants in this investigation were quite symptomatic and none had isolated segments of pneumatosis in the colon. The method of selection may have precluded selection of milder forms of NEC such as pneumatosis coli.

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We conclude that a substantial proportion of neonates with NEC will be of term gestation and present earlier than premature infants with the disorder. In addition, the majority of affected term infants will have been ill. Full-term infants exhibiting one or more of the apparent predisposing

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features we have identified should be watched with a high index of suspicion. Early aggressive management must be undertaken should they develop signs and symptoms of NEC.

Joseph Whitson of the Fort Sam Houston Patient Administration Division and Biostatistics Activity gave assistance in data retrieval.

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CORRECTION

Omissions.—In the Ambulatory Pediatric Association Program and Abstracts, published in the April Journal (1988;142:365-408), the name of a fellowship award and an institutional affiliation were omitted. On page 369, in the "APA Teaching Award" section, the 1988 citation for the Ohio State University should have read as follows: "Ohio State University, Department of Pediatrics, Ambulatory Division, Fellowship in Behavioral—Developmental Pediatrics, Columbus." On page 386, in the abstract entitled "Prevention of Head Injury by Bicycle Helmets: A Field Study of Efficacy," the institutional affiliations should have read as follows: "Harborview Injury Prevention and Research Center, Group Health Cooperative of Puget Sound, and Departments of Pediatrics and Epidemiology, University of Washington. Seattle."

Infection Rates of Broviac-Hickman Catheters and Implantable Venous Devices

Carol L. Wurzel, MD; Karen Halom, RN; Joseph G. Feldman, PhD; Lorry G. Rubin, MD

 We retrospectively identified and prospectively followed up 62 patients with 78 venous-access catheters over a 30-month period (15773 catheter-days) to compare infectious complications of Broviac-Hickman catheters (n = 33) and totally implantable venous devices (n=45) in pediatric oncology patients. Demographic data and characteristics of catheter use were comparable for both groups. Significantly associated with the risk of a catheter-associated infection were (1) the percentage of time the patient was neutropenic and (2) a patient age of younger than 2 years. In the Broviac-Hickman catheter group, 14 catheter-associated infections occurred in 27% of patients using catheters for an Infection rate of 0.21/100 catheter-days. In the implantable venous device group, 13 infections occurred in 24% of patients using catheters for an infection rate of 0.14/100 catheter-days. The relative risk of Infection from Broviac-Hickman catheters compared with implantable venous devices was 1.5, which was not significant (95% confidence interval, 0.7 to 3.2). Thus, the incidence of infectious complications was comparable for both catheter types.

(AJDC 1988;142:536-540)

Subcutaneously tunneled Silastic right atrial catheters (Broviac-Hickman catheters) protrude through the skin and require regular accessing for maintenance of patency1-6; it is not surprising that infectious and nonin-

fectious complications have been reported with their use.7-16 Totally implantable venous devices are also subcutaneously tunneled right atrial catheters that differ from Broviac-Hickman catheters because they have a subcutaneous portal with self-sealing septum that is accessed by needle puncture through intact skin. They require less manipulation and have had lower infectious and noninfectious complication rates than reported for Silastic catheters. 17-22 However, no comparative studies of these two catheter types have been reported. We prospectively compared our experience with Broviac-Hickman catheters and the totally implantable venous devices in a pediatric oncology population.

PATIENTS AND METHODS **Patient Population and Data Collection**

All pediatric oncology patients who received a surgically placed venous-access catheter were identified at time of placement and recorded in a logbook on the pediatric oncology ward. Patients who had a catheter placed between April 1985 and August 1987 were identified, and the occurrence of infection was determined by chart review. Patients were followed up for a minimum of 30 days after placement. Demographic and clinical data and information regarding catheter use were obtained from detailed flow sheets maintained on all oncology patients. Data collection was verified by review of inpatient records for all hospital admissions, the surgical report of the catheter placement procedure, and the microbiology laboratory reports of all positive blood cultures. Demographic, clinical, and laboratory data (Table 1), as well as mechanical catheter complications, catheter-associated and catheter-independent infectious complications (defined below), and episodes of fever were recorded. In addition, percentage of time the patient was neutropenic (defined as the number of weeks in which at least one complete blood cell count showed an absolute granulocyte count $<0.5\times10^{9}/L$ [<500/mm³] divided by the number of weeks the catheter was in place), percentage of days in which the catheter was accessed, and percentage of inpatient days were calculated for all patients.

Clinical Methods

The venous-access catheters used were Silastic subcutaneously tunneled Broviac-Hickman catheters (Evermed), and totally implantable venous devices (Mediport, Infusaport, and Port-a-cath). Choice of catheter type was, in general, by parental discretion following a description of the two catheter types and discussion of advantages and disadvantages of both types in terms of catheter care and patient comfort; comparative infection rates were not discussed as these data were unavailable. Prior to March 1986, only Broviac-Hickman catheters were used. A patient who had a failure with one type of catheter often subsequently received the other type of surgically placed catheter. Patients in whom referral for bone marrow transplantation was anticipated received Broviac-Hickman catheters.

All catheters were placed by pediatric surgeons in the operating room. The Broviac-Hickman catheter dressing was changed once daily in the hospital and on alternating days at home. Implantable venous device dressings were changed every 48 hours by a nurse while the device was in use; the access needles were changed weekly. All patients with fever were admitted to the hospital and examined uniformly. Serum samples for culture were obtained through the venous-access catheter and from a peripheral vein and injected into a 1.5 microbial tube (Isolator). In general, therapy with vancomycin hydrochloride was instituted for patients with adequate neutrophil counts, and vancomycin, ticarcillin disodium, and tobramycin sulfate were given to patients with neutropenia.

An infection was considered definitely

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Table 1.—Patient Population Characteristics and Characteristics of Catheter Placement and Use

| | | ters (n = 33) | Implant Devic | | |
|------------------------------|-----------|---------------------|------------------|---------------------|------|
| | No. (%) | Days Exposure, % | No. (%) | Days Exposure, % | P |
| Age, y | | | | | |
| <2 | 6 (18.2) | 12.5 | 6 (13.3) | 6.7 | |
| 2-10 | 20 (60.6) | 66.2 | 25 (55.6) | 64.4 | .59* |
| >10 | 7 (21.2) | 21.4 | 14 (31.1) | 28.9 | |
| Gender | | | | | |
| % - M - × | 19 (57.6) | 64.7 | 24 (53.3) | 59.0 | .71* |
| F | 14 (42.4) | 35.3 | 21 (46.7) | 41.0 ∫ | 47 % |
| Diagnosis | | | | | |
| Solid tumor | 17 (51.5) | 49.2 | 22 (48.9) | 45.9 | .82* |
| Leukemia | 16 (48.5) | 50.8 | 23 (51.1) | 54.1 | .02 |
| Perioperative antibiotic use | | | | | |
| Yes | 11 (33.3) | 26.5 | 21 (46.7) | 41.8 | .24* |
| No | 22 (66.7) | 73.5 | 24 (53.3) | 58.2 ∫ | 7 |
| V 14 3 3 1 3 1 | m | | 111 | | |

| | | viac-Hickman Catheters | implar i | | |
|--|-----|------------------------------|-------------|----------------------------|------|
| | No. | Mean ± SD | No. | Mean ± SD | P |
| Absolute granulocyte count at placement, × 109/L (/mm³) | 31 | 2.4 ± 2.6 (2488.7 ± 2680) | 45 | 3.2 ± 2.7 (3273 ± 2727) | 22† |
| Time neutropenic, % | 33 | 19.6 ± 23.2 | 45 | 1.2 ± 29.2 | 92† |
| Days accessed, % | 33 | 41.4 ± 21.9 | 45 | 37.2 ± 26.0 | .46† |
| Inpatient days, % | 33 | 38.1 ± 23.3 | 45 | 32.2 ± 38.10 | .33† |
| Days catheter in place‡ Mean | | 200.3 ± 164.2 | | 203.6 ± 138.0 | .42† |

 $^{*\}chi^2$ *P* values shown are based on comparison of the number in the two catheter groups. *P* values based on the distribution of days exposed between patients in the two catheter groups were similar to those shown.

†Student's t test.

catheter associated if fever was present along with a positive blood culture obtained through the catheter and a negative blood culture obtained through a peripheral vein, fever and a positive blood culture from both the catheter and a peripheral vein were present with a fivefold higher colony count from the centrally obtained culture, 23 or local inflammation occurred requiring antibiotic therapy (generally associated with a positive culture). An infection was considered probably catheter associated if fever was present in addition to a positive blood culture with no other focus of infection.

A trial of antibiotic therapy was administered for most catheter-associated infections and was considered successful if catheter removal was not required to resolve signs and symptoms of infection and follow-up blood cultures were negative. Clinically severe infection (septic shock) or continued fever or positive blood cultures beyond 72 to 96 hours of appropriate antibiotic therapy resulted in catheter removal.

Statistical Methods

Comparisons of infection rates were made in several ways. In one approach, rates of infection per 100 catheter-days were compared using binomial or hypergeometric probabilities or both. 24 Stratified analysis used the Mantel-Haenszel-pooled χ^2 statistic after checking for interactions. 25 If significant interactions existed, data were not pooled over strata. These analyses included the occurrences of multiple infections associated with a given catheter.

Multivariate analysis used logistic regression with days of follow-up as a covariate and independent predictor variables with the probability of first infection as the dependent variable. The cumulative probability of remaining infection free was estimated using the product-moment method, with statistical significance assessed by the log-rank test. In the multivariate logistic regression and the product-moment methods, each patient (catheter)

was observed until the first infection. Differences in distributions of frequencies were tested using the χ^2 statistic or Fisher's exact test. Differences in averages were assessed using the Student t test and the nonparametric Mann-Whitney U test.

RESULTS

Seventy-eight venous-access catheters were placed in 65 patients during the study period. There were no significant differences between the Broviac-Hickman catheter group and the implantable venous device group in age, sex, percentage of solid tumors, mean absolute granulocyte count at placement, mean number of days in place, percentage of time the patient was neutropenic, percentage of days accessed, and percentage of inpatient days, either by comparing numbers of patients or days of exposure in each category (Table 1). Thirty-three Silastic catheters (Broviac, 15; Hickman, 18) and 45 totally implantable venous devices (Mediport, 34; Infusaport, ten; and Port-a-cath, one) were placed. There were no significant differences in the infection rate between the two types of Silastic catheters or among the three types of implantable devices. Antibiotics were given prior to 41% of placement procedures, although not generally for prophylaxis of catheterassociated infection. Catheters were in place for an average of 202 days (range, 12 to 647 days, 15 773 catheterdays). One Broviac-Hickman catheter and three implantable venous devices were removed during the first 30 days due to infections or mechanical complications. Twenty-eight catheters were still in place at the end of the study (13 Broviac-Hickman catheters [39%], and 15 implantable venous devices [33%]). Fourteen patients died during the study period: 90% had functioning, uninfected catheters at the time of death.

Twenty-seven catheter-associated infections occurred in 22 catheters; thus, one or more infections developed in 28% of the catheters. Eighty-six percent of catheter-associated infections were considered definite, and 14% probable (see "Clinical Methods" section). All infections were at the exit site (or overlying the portal), were bacteremias, or both; there were no episodes of infection overlying the tun-

[‡]Total days the Broviac-Hickman catheters were in place were 6610; and for implantable vencus devices, 9163.

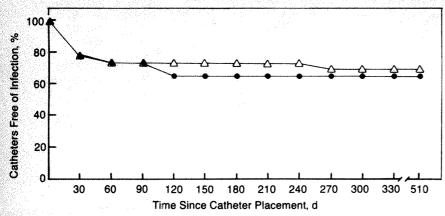


Fig 1.—Comparison of survival curves of Broviac-Hickman catheters (solid circles) and implantable venous devices (open triangles). Survival curve indicates percentage of catheters that remain infection free over time. Given catheter is withdrawn from further analysis after occurrence of first infection in that catheter. Curves are not significantly different (P>.7 by log-rank test).

neled portion of the catheter. In the Broviac-Hickman catheter group, 14 infections occurred during 6610 days; three were local only, and 11 had bacteremia, for an infection rate of 0.21 per 100 catheter-days. In the implantable venous device group, 13 infections occurred during 9163 days, for an infection rate of 0.14 per 100 catheterdays; three were local only and ten had bacteremia. The relative risk of infection of Broviac-Hickman catheters compared with implantable venous devices was 1.5 (95% confidence interval [CI], 0.7 to 3.2), which was not significant. The cumulative risk of first catheter-associated infection over time for each type of catheter was estimated using the product-moment method (Fig 1). Within 30 days, slightly over 21% of the patients developed infection. After two months this increased to 26%, followed by a leveling of the curve. The risk of catheter-associated infection during the first month was three times greater than in the second month (P < .05), and over 100 times greater than after two months (P < .001). Seventy-four percent of catheter-associated infections were cured without catheter removal (eight of 13 in the Broviac-Hickman catheter group, and 12 of 14 in implantable venous device group). Proved or suspected catheter-associated infection was responsible for 10% of inpatient days. The catheter was considered to be the source for all but two

bacteremias during the study period.

The isolates responsible for the catheter-associated infections were as follows: coagulase-negative staphylococci, 11; Staphylococcus aureus, six; enterococci, two; viridans streptococci, one; Neisseria flavescens, one; gram-negative bacilli, four; and Candida albicans, one. There was evidence of local infection in two catheters, but a culture yielded no organism. Thus, 74% of infections were caused by gram-positive cocci. In two instances, simultaneously occurring local infection and bacteremia were noted.

Risk Factors for Catheter-Associated Infection

As was observed for catheter type, there was no significant difference in catheter infection rate for gender (male vs female relative risk of infection, 1.83; 95% CI, 0.81 to 4.20) or use of perioperative antibiotics (relative risk of infection without perioperative antibiotics, 1.70; 95% CI, 0.80 to 3.61). There was an interaction effect between catheter type and both patient age and tumor type (using χ^2 test for interaction and infection rates per 100 catheter-days, data not shown); thus, these factors were analyzed for each type of catheter separately (Table 2). Children younger than 2 years were at higher risk for catheter-associated infection than older children with either catheter type. Additionally, children

younger than 2 years seemed to be at higher risk for infection with a Broviac-Hickman catheter than with an implantable venous device (relative risk, 2.2; 95% CI, 0.60 to 8.21). This is in marked contrast to the older groups where the relative risk for infection from a Broviac-Hickman catheter vs implantable venous device was 1.1 for children aged 2 to 10 years and 0.20 for children older than 10 years (P < .001). The catheter-associated infections as depicted in survival curves (Fig 2) show large differences in infection rates by age. The cumulative probability of infection during the first 30 days after insertion in children younger than 2 years was 55%. Within four months, the probability of infection had increased to 85%. In older children, the cumulative risk of infection increased to about 20% within three months and thereafter did not increase. Children with solid tumors were at lower risk for infection with an implantable device than those with leukemia (Table 2). The percentage of time with neutropenia significantly elevated the risk of infection irrespective of other factors. In the multivariate analysis, percentage of time with neutropenia independently correlated with risk of infection for both types of catheters. For every increase of 10% in time that a patient was neutropenic, their risk of infection increased by a factor of 1.5fold (P < .01). Children younger than 2 years were 5.7 times more likely to develop infection than older children (P < .05). These relationships existed independent of tumor type, percent days accessed, inpatient days, absolute granulocyte count at the time of catheter placement, and gender. None of the latter variables were significant after considering percentage of time with neutropenia and age.

COMMENT

Previous reports have documented an infectious complication rate of 0.10 to 0.68 per 100 catheter-days for Broviac-Hickman Silastic catheters, 1.7-16.28 and 0.05 to 0.18 per 100 catheter-days for implantable venous devices. 17-22 However, claims of lower infection rates are difficult to interpret because there has been only one comparative

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| | No. of Infections | Catheter- Days | Infection Rate/ Catheter-Days | Relative Risk | 95% Confidence Interval |
|----------------|----------------------|-------------------|----------------------------------|------------------|-------------------------------|
| | | Broviac-Hick | kman Catheters | | |
| Patient age, y | _ | | | | |
| <2 | 9 | 827 | 1.09 | 1.00 | |
| 2-10 | 5 | 4371 | 0.11 | 0.10 | 0.04-0.31 |
| >10 | | 1412 | 0.0 | | 0.0-0.53 |
| <2 vs ≥2 | | | | 0.08 | 0.03-0.24 |
| Tumor type | | | | | |
| Leukemia | 6 | 3233 | 0.18 | 1.00 | |
| Solid | 8 | 3355 | 0.24 | 1.28 | 0.45-3.70 |
| | | implantable ' | Venous Devices | | |
| Patient age, y | | | | | |
| <2 | 3 | 613 | 0.49 | 1.00 | |
| 2-10 | 6 | 3847 | 0.10 | 0.21 | 0.05-0.83 |
| >10 | 4 | 2653 | 0.15 | 0.31 | 0.07-1.38 |
| <2 vs ≥2 | 1 1 4 | | | 0.24 | 0.07-0.86 |
| Tumor type | | | | | |
| Leukemia | 11 | 4210 | 0.26 | 1.00 | |
| Solid | 2 | 4953 | 0.04 | 0.15 | 0.03-0.70 |

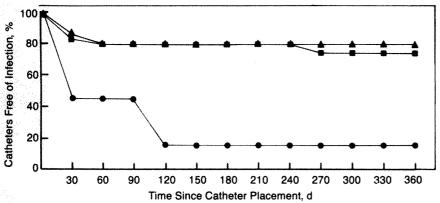


Fig 2.—Comparison of survival curves of catheters in different patient age groups. Survival curve indicates percentage of catheters that remain infection free over time. Given catheter is withdrawn from further analysis after occurrence of first infection in that catheter. Data for both catheter types are combined. Curve for age younger than 2 years is significantly different from those representing older age groups (P<.001 by log-rank test). Solid triangles indicate patient aged older than 10 years; solid squares, between 2 and 10 years; and solid circles, younger than 2 years.

study, a preliminary report of an ongoing randomized prospective comparative study of the two catheter types in adult oncology patients. Skelton and coworkers²⁹ found no statistically significant difference between the infection rate for Hickman catheters and implantable venous devices; there was a trend toward a higher rate in the Hickman catheter group. Thus, our prospective comparative study, which found no significant difference

in infection rate (0.21 per 100 catheter-days for Broviac-Hickman catheters vs 0.14 per 100 catheter-days for implantable venous devices, Fig 1) for these two catheter types, is the first large comparative study and our findings contrast with previous conclusions. Children younger than 2 years had a significantly higher rate of infection than older children, and in this subgroup there was a higher risk of catheter-associated infection with the

Broviac-Hickman catheter than with implantable venous devices. This makes biologic sense as the external catheter segment of the Broviac-Hickman catheter may be contiguous to the diaper area of these small children and be at increased risk for external contamination. The only other identified independent risk factor for infection was the percent time with neutropenia, which likely reflects the intensity of chemotherapy. The frequency of mechanical catheter complications was also similar for both catheter types (data not shown).

As our patients were not randomized to receive one or the other catheter type, unrecognized biases of group differences may have influenced our results. However, the two patient groups were comparable in demographic and laboratory characteristics (Table 1). The criteria for catheter infection were objective, since almost all patients had a positive blood or wound culture. Complete ascertainment of all catheter placements as well as of all infectious episodes seems likely since all information was verified by checking inpatient records, ambulatory flow sheets, and clinical microbiology reports.

Fifty-nine percent of all catheterassociated infections occurred within the first 30 days of catheter placement. Catheters were often placed when patients were receiving intensive induction chemotherapy or being treated for a complication of their disease or therapy. Perioperative antibiotics were not administered unless another indication for antibiotic use such as fever and neutropenia was present; in most cases, they were not directed against organisms that commonly cause infections to develop in catheters (eg, vancomycin was not used as a perioperative antibiotic). It is possible that appropriate prophylactic antibiotics or continuous antibiotic prophylaxis for the first month may decrease the high infection rate observed during the first 30 days of placement.

In the current study, the majority of catheter-associated infections were eradicated without catheter removal. Cure rates for infected patients with Broviac-Hickman catheters were similar to those for patients with implantable venous devices and comparable with previous studies. 7,14,20,23,29 Administering antibiotics through an infected catheter may prolong catheter

survival.³⁰ On the other hand, long courses of antibiotic therapy for treatment of catheter-associated infections may prolong hospitalization; in the current study, 10% of hospital days

were directly related to catheter associated infections.

Lillian Carmody, RN, assisted in data compilation and Ann Fabiochi prepared the manuscript.

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Epidemiology of the Early Amnion Rupture Spectrum of Defects

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· We used data from the populationbased Metropolitan Atlanta Congenital Defects Program to study the epidemiology of the early amnion rupture spectrum of defects. For the period 1968 through 1982, we identified 45 patients among 388325 live births, for a birth prevalence rate of 1.16 per 10 000. The prevalence for male infants was 0.91 and for female infants, 1.44. The defects occurred 1.76 times more often in blacks than in whites (95% confidence interval 0.98, 3.13). Infants of young, black multigravidas (<20 years, more than one pregnancy) showed the highest rate (6.2), and infants of older, black multigravidas showed the lowest rate (0.5) (rate ratio = 12.4, 95% confidence interval 4.2, 36.4). These findings suggest that young, black multigravidas are at much higher risk than are older, black multigravidas of having infants with this spectrum of defects. Ascertainment (diagnostic) differences between hospitals probably account for some of the racial discrepancy in birth prevalence, but they do not explain the maternal age effects in black multigravidas. Because the higher rates for blacks probably reflect more accurate diagnoses, the findings also suggest that a closer estimate of the true birth prevalence may be about 3 per 10 000 live births.

(AJDC 1988;142:541-544)

The early amnion rupture spectrum (TEARS) of defects is a variable nonrandom occurrence of major struc-

tural anomalies. The mechanism appears to involve rupture of the amnion. with chorion intact, and the subsequent production of fibrous bands or a constrictive uterine environment or both from the loss or resorption of amniotic fluid.1.2 This sequence can affect morphogenesis and lead to anomalies of the limb, trunk, or craniofacial structures. The spectrum of anomalies from early amnion rupture is large and includes the following: (1) extremities: limb reductions, amputations. constrictions. syndactyly. pseudosyndactyly, polydactyly, hypoplasia, distal lymphedema, foot deformations, and hip dislocation; (2) craniofacial: anencephaly, gross facial distortion, unusual facial clefting, eye, ear, nose defects, encephalocele, cleft lip, cleft palate, choanal atresia, craniostenosis, and oligohydramnios deformation sequence; and (3) other: placental or amniotic band attachment to body parts, abdominal or thoracic wall defects, ectopia cordis, evisceration, gastroschisis, omphalocele, short umbilical cord, and scoliosis.

The nature and severity of the anomalies relate to the timing of the event. No two fetuses are identically affected, and no single feature consistently occurs. The combination of defects has been given many names, including amniotic band syndrome, amniotic band disruption complex, aberrent tissue bands, and ADAM complex (amniotic deformity, adhesion, mutilations). Because there is still no general consensus on the most appropriate name for this combination of defects, we use the acronym TEARS of defects, taken from that described by Smith. The acronym describes the initiating pathologic event and indicates a wide phenotypic spectrum of defects.

Little is known about the epidemiology of this complex of defects, and reported results of case series have suggested a frequency of between 1 per 1200 and 1 per 15 000 live births.14 We describe the epidemiology of TEARS in Atlanta over a 15-year period (1968 through 1982) using data from the Metropolitan Atlanta Congenital Defects Program (MACDP).

METHODS

The MACDP is a population-based birth defects surveillance system that has been in operation since 1968. It is a joint program of the Centers for Disease Control, the Georgia Mental Health Institute, and the Emory University School of Medicine. Atlanta. The program monitors the occurrence of birth defects to residents of the five-county metropolitan Atlanta area and covers approximately 27000 births per year. Patients registered are all infants born with structural, chromosomal, or biochemical abnormalities that are diagnosed by age 1 year. Ascertainment of patients is from review of hospital records of newborns, delivery room logbooks, autopsy reports, pediatric admissions, and results of cytogenetics testing. These data are supplemented by review of birth certificate data from the Georgia Department of Human Resources. The hospital records of newborn patients and their mothers are reviewed for clinical information and demographic data. Because of adequate followup we believe that ascertainment of major defects is very high. Details on the MACDP are available elsewhere. 5,6

We reviewed all records of infants with birth defects ascertained between 1968 and 1982. For analysis, we selected records from MACDP of infants who had a diagnosis of amniotic bands. We also reviewed MACDP records of infants with any of the previously mentioned spectrum of anomalies from early amnion rupture. Our reasons for this review included (1) the fact that the code for amniotic bands was not always recorded from the patient record

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| | Ra | ite per 10 000 Live Birt (No. of Patients) | hs |
|--|-----------|---|-----------|
| | White | Black | Both |
| Sex M | 0.75 (10) | 1.23 (8) | 0.91 (18) |
| F | 1.12 (14) | 2.06 (13) | 1.44 (27) |
| Total | 0.93 (24) | 1.64 (21) | 1.16 (45) |
| Maternal age, v | | | |
| <20 | 1.37 (5) | 3.27 (12) | 2.32 (17) |
| 20-24 | 0.97 (8) | 1.16 (5) | 1.03 (13) |
| 25-29 | 0.83 (7) | 0.69 (2) | 0.79 (9) |
| 30-34 | 0.73 (3) | 1.49 (2) | 0.92 (5) |
| >34 | 0.83 (1) | | 0.58 (1) |
| Primigravida | | | |
| Maternal age group, y <20 | 1.80 (5) | 2.33 (6) | |
| ≥20 ≥20 | 1.03 (9) | 2.10 (6) | |
| Total | 1.22 (14) | 2.21 (12) | |
| Selected and Campaignal Control of the Control of t | 1.22 (14) | Z.E. (12) | ••• |
| Multigravida Maternal age group, y | | | |
| <20 | | 6.22 (6)† | |
| ≥20 | 0.79 (10) | 0.50 (3) | * * * |
| Total | 0.75 (10) | 1.30 (9) | *** |

*TEARS indicates the early amnion rupture spectrum.

†Black multigravidas aged <20 y vs ≥20 y (rate ratio = 12.4, 95% confidence interval 4.2, 36.4).

form and (2) the possibility that physicians recording defects in the hospitals might not have recognized the clustering of defects as probable TEARS. We then selected from those reviewed records only the infants who had combinations of two or more defects that were consistent with the previously mentioned early amnion rupture spectrum. We determined and compared birth prevalence rates for available demographic variables such as sex, race, maternal age, maternal gravidity and parity, hospital, and year of birth.

We calculated rates per 10000 live births for all demographic variables mentioned above and confidence intervals (CI), using tabular values for estimates of a Poisson-distributed variable. We tested trends by maternal age and race with an extended Mantel-Haenszel χ^2 statistic and calculated CIs for the rate ratios using Miettinen's test-based approximation.

RESULTS

From January 1968 through December 1982, a total of 45 patients with clinically diagnosed anomalies of TEARS were ascertained in metropolitan Atlanta. In all infants, extremities were affected: upper or lower extremities, or both, but in 27 infants (60%) only limbs were affected. Ten infants (22%) had limb and craniofacial defects only. Three infants (7%) had

limb and abdominal wall or visceral defects only. Five infants (11%) had limb, craniofacial, and abdominal wall or visceral defects. In descending order, the defects most commonly mentioned were (1) limb amputation or constriction: (2) cleft lip, cleft palate, or both; (3) eye defects; and (4) nose defects or encephalocele.

These 45 patients were ascertained among 388 325 live births, for a birth-prevalence rate of 1.16 per 10 000 live births (Table). The rate for male infants was 0.91, and the rate for female infants was 1.44. The rate for blacks was 1.76 times higher than for whites (95% CI 0.98, 3.13). The racial difference was slightly greater for female than for male infants.

When we stratified maternal age into five-year intervals, we found a decreasing trend in the rate of TEARS by maternal age (Table). The risk of having infants with TEARS was 2.3 times, or greater, for mothers under the age of 20 years than for mothers in any of the older age groups (extended Mantel-Haenszel $\chi^2 = 5.03$, P = .02). When we examined this maternal age difference by race, it remained statistically significant only for blacks; the risk was 2.2 times, or

greater, for mothers younger than 20 years than for mothers in any of the older age groups (extended Mantel-Haenszel $\chi^2 = 5.32$, P = .02). By maternal age strata, the racial difference in rates was greatest for the under-20year group. Blacks had a rate of 3.27, and whites had a rate of 1.37 (rate ratio = 2.4, 95% CI 0.87, 6.56). Because the rates in the age groups 20 years and older were similar, we grouped them together to compare with the youngest age group (<20 years). The risk was 2.6 times greater (95% CI 1.44, 4.61) in the younger than in the older mothers. In controlling for race, this maternal age difference was statistically significant only for blacks; the risk was 3.3 times greater (95% CI 1.46, 7.46) in the younger than in the older black mothers.

Within the two maternal age groups, neither gravidity nor parity accounted for a significant difference in blacks or whites. In controlling for gravidity, however, the Table shows the rate to be 12 times (95% CI 4.2, 36.4) higher in the black multigravidas (more than one pregnancy) under the age of 20 vears than in those over the age of 20 vears. In comparison, there were no affected infants born to the under-20year-old white multigravida group. Likewise, in controlling for parity (numbers not shown), the rate was 11 times (95% CI 3.5, 34.4) higher in the younger, black multiparous (more than one birth) mothers than in the older, black multiparous mothers. We did not see this apparent maternal age effect in primigravidas or primiparous moth-

Sixty-two percent (13) of the black and 42% (ten) of the white patients had a birth weight under 2500 g compared with the observed low birth weight rates for live births in Atlanta of 13% for blacks and 6% for whites. Mean gestational age of these newborns was 36 weeks. Seventeen of the infants were known to have died by the time of patient ascertainment, for a case-fatality rate of 38%. Twelve of those 17 died in the first day of life. Multiple defects were more likely to be fatal. Of 25 infants with only limbs affected, three died (12% rate); of 20 with multiple structures affected, 14 died (70% rate). Karyotypes were reported on six patients, and these were normal. Each MACDP patient record was reviewed for any mention of a family history of amniotic bands or similar defects. We found no such history for any patient. Neither did we find a secular trend nor a significant seasonal trend by last menstrual period or by time of birth.

Twenty-two (49%) of all patients and 16 (76%) of black patients were born and had their defects diagnosed at one large city hospital, hospital A. The rest were evenly distributed among ten other hospitals. For both races the frequency of occurrence at hospital A was three times higher than at other hospitals (P < .01). Also at that hospital, the overall rate differences for blacks by maternal age were noted. though at a less significant level (P=.07). However, the maternal age effect among the black multigravidas remained statistically significant (P = .0007). The distribution of the 388 325 Atlanta live births (the denominators) was such that 58% of blacks and 5% of whites were delivered at hospital A. For mothers under the age of 20 years, however, 81% of blacks and 14% of whites were delivered at hospital A. For mothers over the age of 20 years, 48% of blacks and 4% of whites were delivered at hospital A.

COMMENT

The early amnion rupture spectrum of defects comprises combinations of defects that occur in the same infants more often than can be attributed to chance, and they relate to amnion rupture and, often, to amniotic bands. The spectrum of anomalies described herein is similar to that reported in the literature. To our knowledge, this is the first population-based study of TEARS. In our literature review we found many case series reports^{3,4,9-27} and one article in which the epidemiology based on such reports was reviewed briefly.28

The prevalence of TEARS at birth has been estimated to be from 1 per 1200 to 1 per 15000 live births.14 The sex and race distribution has not shown a predisposition. The defects of TEARS are thought to occur sporadically, though there are reports of a few patients whose defects were ap-

familial.29-31 Our parently showed an overall birth prevalence of TEARS in Atlanta of 1.16 per 10000 births. A difference was seen by sex and race, with a slightly greater frequency in newborn females and blacks.

An unexpected finding was that young maternal age, especially among black multigravidas, appeared to be a significant risk factor. This maternal age effect was not seen in black primigravidas or in white mothers. In one study of 24 patients in 1977,3 the authors suggested that young maternal age was possibly important, but most investigators have not made this observation. Recently, multigravidity has also been suspected of being related to the occurrence of these defects.32 The results of our study suggest that young, black multigravida mothers are at much higher risk than are older, black multigravidas mothers of having infants with this spectrum of defects.

The high proportion among our patients of babies with low birth weight is related to the number of preterm deliveries and the number of infants having sustained amputations. Although few were done, karyotypes were reported to be normal, and there were no familial defects reported. We also did not observe any seasonal differences, either by time of last menstrual period or by time of birth. These findings are similar to those of other studies.

The case-fatality rate is high, and the babies with multiple defects have a higher death rate. Previous authors have suggested that the earlier in gestation the amnion ruptures, the greater the likelihood of more severe defects, spontaneous abortion, stillbirth, or early postnatal death. 1,2,4,18 The gestational prevalence (number of occurrences per number of gestations) of amnion rupture defects, then, is probably much higher relative to the birth prevalence. A review of 175 unselected stillborns in Wisconsin showed a 3% occurrence,33 and a review of 813 previable fetuses (gestational age ≤20 weeks) in British Columbia showed a 1.5% occurrence.34 Survivors, on the other hand, that is, those seen in the clinical setting, tend to have defects predominantly affecting limbs, and fewer other severe defects. 1,2,18

Our findings must be considered in the light of certain limitations. The MACDP surveillance system relies on physicians' examinations and documentation of findings. Differences among physicians' examinations and their diagnostic abilities may lead to a selection or recognition bias. Our observation that these defects occurred three times more frequently at hospital A than at other hospitals, and, therefore, more in blacks than in whites, may reflect this potential bias. Many previous authors have reported on the difficulty of diagnosing this spectrum of defects and have suggested that from one half to two thirds of all patients have their conditions misdiagnosed. 1-4,13,16,18,28 Because hospital A has a staff of dysmorphologists and clinical geneticists, we believe that patients in hospital A had a better chance of having their conditions diagnosed correctly. Conversely, patients in the other hospitals may well have been underascertained. If this explained the racial difference, it would also suggest that a more accurate estimate of the birth prevalence of TEARS would be found in hospital A, about 3 per 10 000 births.

An alternative explanation, if we assume no recognition bias, is that the occurrence of TEARS differs between the populations using hospital A and those using other hospitals. Since hospital A serves mostly a young, black, low-socioeconomic population, these or related factors may be important in the occurrence of TEARS. Selection bias, however, would not explain the strong maternal age effect among black multigravidas, as this phenomenon was observed in hospital A. The relatively small number of patients suggests, rather, that the prevalence rates may be unstable, which calls for caution in interpretation.

In summary, the epidemiology of TEARS in Atlanta suggests that young, black multigravida mothers may be at high risk for having newborns with these defects. To our knowledge, this has not been reported before. We suggest that this association be studied further, along with the possibility for an association with biologic events affecting the integrity of the amnion, such as infections during

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gestation. The crucial issue is to identify factors that lead to early amnion

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Quotables:

Writing: I think I did pretty well, considering I started out with nothing but a bunch of blank paper.

STEVE MARTIN

Special Features

Radiological Case of the Month

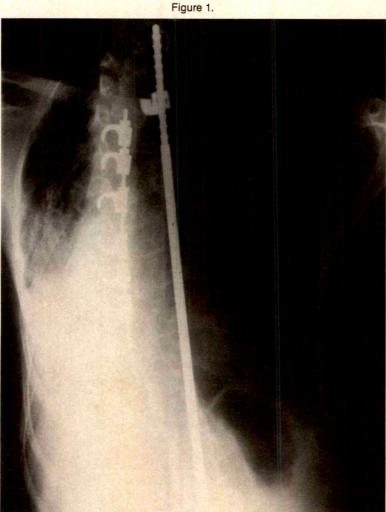
Andrew A. Colin, MD, Julian L. Allen, MD, Charles B. Berde, MD, PhD, N. Thorne Griscom, MD, John E. Hall, MD (Contributors); Lionel W. Young, MD (Section Editor)

Accepted for publication Oct 10, 1986. From the Divisions of Respiratory Diseases (Drs Colin and Allen), Anesthesia (Dr Berde), Radiology (Dr Griscom), and Orthopedics (Dr Hall), Harvard Medical School and The Children's Hospital, Boston.

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At age 12 years, a young man underwent posterior vertebral fusion with Harrington distraction and compression rods for correction of progressive thoracic scoliosis diagnosed when he was 8 years old. Four years after the operation, breath sounds on auscultation were decreased over the right lower portion of the chest, and roentgenography demonstrated a collapsed

right lower lobe (Fig 1). The slow but progressive decrease in ventilatory function required corrective vertebral operation at age 21 years, in an attempt to obtain a mild kyphosis rather than the marked thoracic lordosis that followed his first vertebral fusion. Respiratory difficulty persisted, and the collapsed lobes in the right lung did not reexpand.



Denouement and Discussion

Bronchial Compression and Ventilatory Dysfunction in Scoliosis

Fig 1.—Anteroposterior chest x-ray film shows inflated left lung and right upper lobe and collapsed right lower lobe.

Fig 2.—Xenon Xe 133 ventilation scan shows ventilation of left lung and complete absence of ventilation of right lung.

Fig 3.—Chest computed tomographic scan shows vertebral body impingement on right main bronchus, causing partial collapse of lumen.

Fig 4.—Postoperative computed tomographic scan shows resected vertebral body. Bronchus is still partially collapsed.

Figure 2.

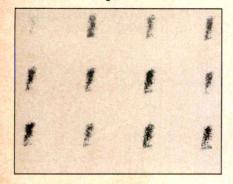


Figure 3.

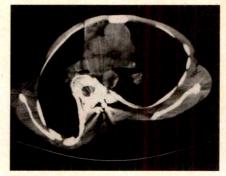
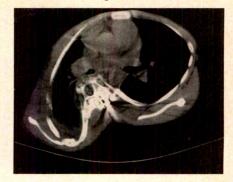


Figure 4.



A xenon Xe 133 ventilation scan (Fig. 2) showed absence of ventilation of the whole right lung, including the aircontaining upper lobe. A computed tomographic (CT) scan (Fig 3) showed that the rotated vertebral bodies impinged on the right main bronchus and caused complete obstruction of its lumen in the CT scan slice 1 cm below. Bronchoscopy confirmed this finding, but whether structural damage to the bronchus existed could not be determined. Subsequent operation consisted of partial anterior resection of the vertebral bodies T-3 through T-8 and right middle and lower lobectomy for bronchiectasis. Ventilatory function still did not improve. Postoperative bronchoscopy showed abnormal collapsibility of the bronchus.

One of the major effects of severe scoliosis is the alteration of lung mechanics due to a decrease in lung vol-

ume.1 Scoliosis accompanied by substantial thoracic lordosis has been shown to produce more respiratory compromise than ordinary kyphoscoliosis with minimal lordosis.2 In the presence of hypokyphosis (nearly flatback), the Harrington compression system, while helping to stabilize the spine, may maintain or increase the lordosis and further affect pulmonary function.3 This compromise of ventilation is attributed to the diminished anteroposterior thoracic dimension and the resulting associated decrease in lung volume. Direct compression of bronchi by vertebral bodies following Harrington rod replacement was shown by Karroll et al.4 In our case, bronchoscopy showed evidence of bronchomalacia, ie, an easily collapsible bronchus that could not maintain patency despite operative resection of the vertebral bodies responsible for

the bronchial compression. A CT scan (Fig 4) showed partial bronchial occlusion, and complete obliteration was shown 1 cm below this segment. In the completely occluded regions of the lung, atelectasis and bronchiectasis developed and operative removal of those segments was required.

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Radiological Case of the Month

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A 2½-year-old boy was referred to the Children's Hospital of Pittsburgh with a history of wheezing, mild fever for two weeks, and abnormal chest roentgenographic findings. He had been in relatively good health, but from age 4 months he had had several episodes of wheezing that improved

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Reprint requests to Department of Radiology, Children's Hospital Medical Center of Akron, 281 Locust St, Akron, OH 44308 (Dr L. W. Young). and resolved with bronchodilator therapy. On admission, the boy was febrile, tachypneic, and wheezing loudly. The right side of his thorax was bulging, and decreased breath sounds were present over his right lung. He had a leukocyte count of 16×10^9 /L ($16\,000$ /mm³), a hemoglobin value of $111\,$ g/L ($11.1\,$ g/dL), and a hematocrit value of $0.34\,$ (34%). His serum electrolyte levels and urinalysis findings were normal. Anteroposterior and lateral roentgenograms of the thorax were obtained (Figs 1 and 2). A drainage

tube was inserted in the right side of the thorax from which 920 mL of purulent material was obtained.

Culture of the fluid from the drainage tube yielded *Haemophilus influenzae*. Blood cultures yielded no pathogens. After nine days of antibiotic therapy, the child was afebrile and asymptomatic, but cystic distention of the right upper hemithorax was even more apparent. Because the drainage tube had a persistent air leak, operative exploration for a suspected bronchopleural fistula was necessary.

Figure 1.

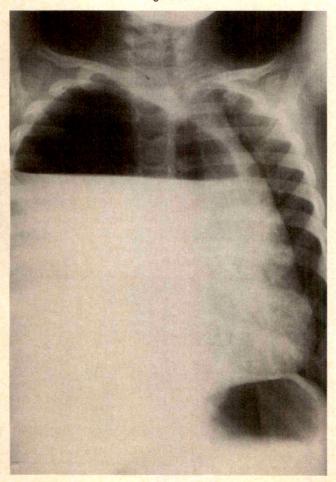
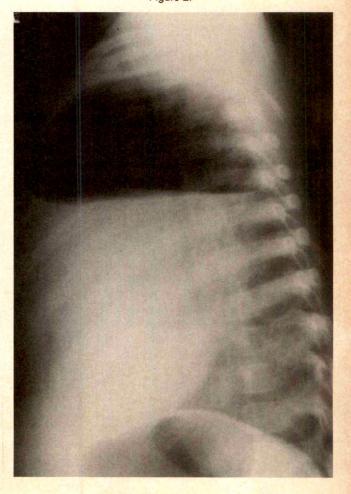


Figure 2.



Denouement and Discussion

Bronchogenic Cyst Infected With Haemophilus influenz

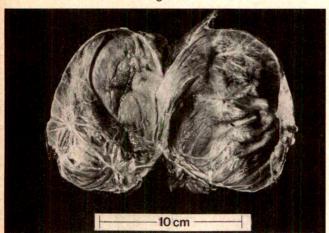
Fig 1.—Anteroposterior roentgenogram of thorax shows cystic distention of right hemithorax with wide air fluid level and displacement of mediastinum and heart to left side.

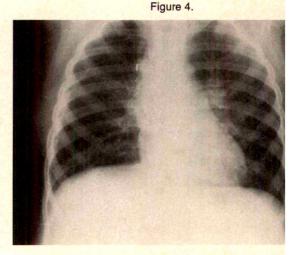
Fig 2.—Lateral roentgenogram of thorax shows air fluid level in right hemithorax.

Fig 3.—Photograph of operative specimen shows trabeculated and thinly septated internal surface of large cyst.

Fig 4.—Anteroposterior roentgenogram of thorax shows full distention of lung after right upper lobectomy.

Figure 3





Operative exploration of the right hemithorax showed a large cyst of the right upper lung for which a right upper lobectomy was done. The pathologic diagnosis was bronchogenic cyst. The patient did well postoperatively. The drainage tube was removed after 15 days, and the chest roentgenogram (Fig 4) one day later showed full distention of the remaining right lung. He was discharged and has had no difficulty during follow-up.

Bronchogenic cysts are lesions of congenital origin derived from primitive foregut. The cysts are formed from abnormal budding or abnormal branching of the tracheobronchial tree. Intrapulmonary cysts are probably the result of late abnormal budding, while mediastinal cysts and cysts in the region of the carina occur early in the embryologic development of the tracheobronchial tree. Most cysts occur in the lungs and mediastinum, but they can separate from the airway and migrate to subdiaphragmatic areas or to the neck. Only histologically can bronchogenic cysts be differentiated from other cystic structures such as bronchial cleft cysts. 1-4

Bronchogenic cysts are usually single and rarely multiple. They tend to

be spherical or ovoid with a thin wall. Trabeculation can be found within the cysts, which may contain multiple, thin septae as in the present case (Fig 3). Histopathologically, bronchogenic cysts contain one or more of the tissues found in the respiratory tree and, characteristically, are lined by pseudostratified columnar epithelium. The walls of the cysts consist of fibrous connective tissue and may contain glands, cartilage, smooth muscle, and elastic fibers. 1-4

Bronchogenic cysts, if uncomplicated, are frequently asymptomatic. They may present, as in the present case, with a history of dyspnea, cyanosis, or unexplained hemoptysis. If a communication exists between the cyst and the tracheobronchial tree, the cyst may fill with stagnant secretions that may become infected, as in the present case. Patients with infected cysts have respiratory distress and almost always symptoms of pulmonary infection, namely, chills, fever, chest pain, and cough. Dullness to percussion and decreased breath sounds may occur over the affected area.5

Roentgenographically, genic cysts are smooth, solitary masses. They are usually homogeneous in density, but occasional fluid level is present in the cy the present case. Intrapu cysts usually occur in the low while mediastinal cysts comn cur in proximity to the tra major bronchi. The major bro the esophagus may be displ the mass. The cysts are usuall to a single lobe and do not much in size.6

An infected bronchogenic quires excision and antibiot ment. If the bronchogenic c incidental radiologic finding a patient is asymptomatic, tr may not be required.4,5

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Under no circumstances should this vaccine be administered parenterally.

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persistent vomiting or diarrinea.

ORIMUNE must not be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome. Further, ORIMUNE must not be administered to patients with altered immune states such as those occurring in thymic abnormal-ities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antime tabolites, or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. IPV is preferred for immunizing all persons in

PRECAUTIONS

Other viruses (including poliovirus and other enterovirus) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may

interfere with the replication of the attenuated strains of poliovirus in the vaccine. It would seem prudent not to administer TOPV shortly after Immune Serum Globulin (ISG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If TOPV is given with or shortly after ISG, the dose probably should be repeated after three months, if immunization is still indicated. However, ISG may not interfere with immunization with TOPV.

The vaccine is not effective in modifying or preventing cases of existing and/or

incubating poliomyelitis.

Use in Pregnancy: Although there is no convincing evidence documenting adverse effects of either TOPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, TOPV is recommended.

(See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS

ADVERSE REACTIONS

Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine.

(See, for example, CONTRAINDICATIONS) and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccine viruses are shed in the vaccine. nee's stool for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relation ship exists. The risk of vaccine-associated paralysis is extremely small for vaccinees, susceptible family members, and other close personal tacts. However, prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis. The Centers for Disease Control report that during the years 1969 through 1980 approximately 290 million doses of TOPV were distributed in the United States. In the same 12 years, 25 "vaccine-associated" and 55 "contact vaccine-associated" paralytic cases were reported. Twelve other "vaccine-associated" cases have been reported in persons (recipients or contacts) with immune deficiency conditions. These statistics do not provide a satisfactory basis for estimating these risks on a per per-

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccineassociated paralysis can be minimized by giving these adults three dose of IPV a month apart before the children receive ORIMUNE. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The Immunization Practices Advisory Committee of the US Public Health Service states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme resits of OPV are cited diverse in the contained of the contained of

rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The Immunization Practices Advisory Committee has concluded that "Oral

polio vaccine remains the vaccine of choice for primary immunization of Children."



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An Analysis of Revenues and Expenses in a Hospital-Based Ambulatory Pediatric Practice

Jay E. Berkelhamer, MD, Kenneth J. Rojek, MBA

 We developed a method for analyzing revenues and expenses in a hospitalbased ambulatory pediatric practice. Results of an analysis of the Children's Medical Group (CMG) at the University of Chicago Medical Center demonstrate how changes in collection rates, practice expenses, and hospital underwriting contribute to the financial outcome of the practice. In this analysis, certain programmatic goals of the CMG are achieved at a level of just under 12000 patient visits per year. At this activity level, pediatric residency program needs are met and income to the CMG physicians is maximized. An ethical problem from the physician's perspective is created by seeking profit maximization. To accomplish this end, the CMG physicians would have to restrict their personal services to only the better-paying patients. This study serves to underscore the importance of hospitalbased physicians and hospital administrators structuring fiscal incentives for physicians that mutually meet the institutional goals for the hospital and its physicians.

(AJDC 1988;142:551-554)

The impact of an ambulatory program on the overall financial performance of a hospital is an essential component of the strategic planning process. Program profitability from the perspective of participating physicians, however, is equally important for determining priorities for clinical departments of a medical school. In 1983, Jennings and Krentz¹ described a series of steps for developing a financial model to perform sensitivity analyses on proposed hospital program changes. Some medical centers have reorganized hospital-based clinics into systems that more closely parallel private group practice.2-9 These new program structures, coupled with increased emphasis on the orderly and efficient management of hospitalbased practices, have resulted in physicians and managers seeking to reduce costs,10 improve physician activity,11 and maximize profits.12 The analysis described in the present report details a method used to estimate profit maximization from the perspective of the Children's Medical Group (CMG) practice at Wyler Children's Hospital at the University of Chicago.

The CMG practice described by Berkelhamer et al¹³ is a separate hospital cost center in which the physician's practice income (profit) is the result of controlling both revenues and expenses for the cost center. Although the hospital maintains a contribution to the cost center in the form of subsidized overhead expenses, improvements in financial performance over a negotiated base are credited to the physician's income and transferred to the clinical department. The physician's income is included as part of the pediatric department's income sharing program and provides a direct financial incentive to the otherwise salaried faculty members to maximize income from their clinical practice.

The CMG provides continuous primary care services, including health maintenance and illness-related care, to approximately 5000 patients making a total of 14000 visits per year. The group's physicians consist of both fully trained faculty members and pediatric residents, all of whom participate in providing direct service to patients. Residents are divided among team sessions four afternoons per week, and are directly supervised by the faculty. At all other times, the practice is staffed by the faculty pediatricians. A medical student is assigned to work with each faculty member at times when residents are not participating in the team sessions. Faculty physicians are available 24 hours a day, seven days a week to provide medical advice or emergency care to their patients. Regular practice hours are 8 Am to 5 PM Monday through Friday and 8 AM to noon on Saturdays. Patients are routinely seen on an appointment basis, but as many as 15% of the visits are "walk-ins" for acute illness management. Charges for services rendered are set at community rates and determined by the faculty pediatricians in consultation with their business manager. During this study, the practice staff consisted of eight faculty members, 22 residents, one nurse-practitioner, a business manager, and six support personnel.

MATERIALS AND METHODS

Practice revenues were intially calculated for an entire fiscal year by type of provider (residents, nurse-practitioner, and faculty) using hospital data sources. Collected revenue by provider type was determined using hospital finance department data on collection rates by payer codes. Practice expenses were then separated into fixed and variable components. Expenses per visit were categorized as space rental, personnel costs, direct fixed costs, and direct variable costs. Finally, practice financial performance was modeled at various activity levels to determine optimal program size and configuration from the perspective of the participating physicians.

Assumptions used for modeling practice performance were adopted from guidelines developed over several years of experience

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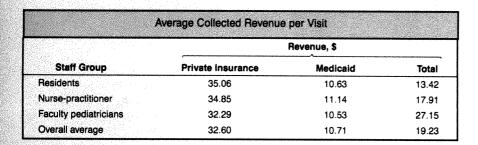
at the medical center. These guidelines reflect time-measured work activities for each job category and judgments made by managerial staff to assure efficient patient care. Staffing patterns were reviewed by the practice faculty so as to attest to their

reasonableness. Assumptions used in modeling were as follows: (1) 1.0 nurse-practitioner was needed for a practice level of over 12000 visits per year; (2) 0.5 nurse's aid was required for every 3000 visits per year; (3) 0.5 secretary was required per

1750 visits; and (4) 0.5 business manager was required for every 12000 visits per

Incremental increases in staffing were not considered at a level of less than 1.0 for nurse practitioners and 0.5 for others. It was the opinion of the practice group that staffing increases of smaller increments were not practical from the point of view of job recruitment and satisfaction. Nevertheless, although smaller incremental staffing changes would have the effect of "smoothing out" the slope of changes in practice performance, general trends sought by this analysis would not be affected.

For the practice analysis, fixed costs were defined as those primarily related to



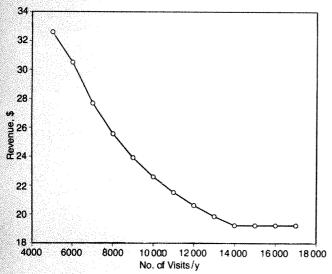


Fig 1.—Collected revenue per visit at various activity levels.

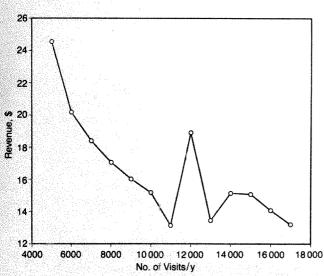


Fig 3.—Expense less collected revenue per visit at various activity levels

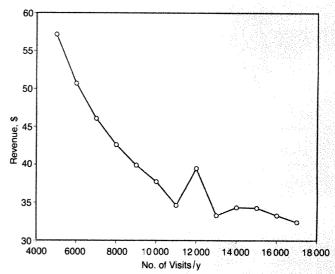


Fig 2.—Expense per visit at various activity levels.

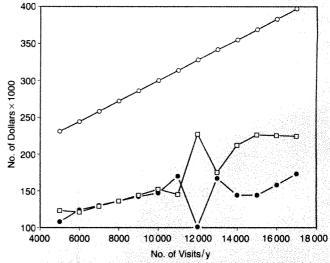


Fig 4.—Relationship of hospital contribution, practice expense less revenue, and professional income to clinical department at various activity levels.

the occupancy cost charged by the hospital to the CMG, which was set at a negotiated rate of \$25 per square foot per year. Fixed costs included facility rental, utilities, housekeeping, and other occupancy expenses, including indirect support services provided by the hospital. These indirect support services included accounting, security, patient billing, and other general operational activities of the entire medical center. Variable costs included all practice supplies, vaccines, drugs and medications, and other similar items directly related to the CMG practice. Personnel costs, which were the largest expense items in the practice, had similarities to both fixed and variable expenses, since these costs increased or decreased in a stepwise fashion with practice volume. Over a relatively small patient volume change, personnel costs behaved as fixed expenses. Over a larger volume range, these costs behaved as variable expenses, as personnel must be added to provide services to a greater volume of patients.

The practice group also noted that increases in activity levels would not likely result in an appreciable change in payer mix, with roughly equal numbers of Medicaid and privately insured patients entering the practice with an overall size increase. This assumption was based on the experience of the practice group in attracting new patients. The competition for new patients in the community served was viewed as formidable, and marketing efforts targeted to privately insured patients could only be expected to maintain the overall practice size. To actually increase the practice size, only a broader approach that would include adding new Medicaid patients was viewed as realistic. However, decreasing the activity of the practice could significantly change the payer mix since Medicaid patient visits might be selectively reduced while the current level of privately insured patients was maintained or even increased slightly.

RESULTS

During the fiscal year analyzed, there was a total of 14 109 visits, with 7311 to residents, 1134 to the nurse-practitioner, and 5664 to faculty members. Eighty-eight percent of the visits to residents, 71% to the nurse-practitioner, and only 24% to the faculty were paid for through the Illinois Medicaid program. Overall, 39% of the patients seen had private insurance of various types, while 61% had Medicaid funding.

The Table demonstrates that pri-

vate-pay patients generated an average of \$32.60 in collected revenue per visit while Medicaid patients generated \$10.71. Overall, each visit generated \$19.23 in collected revenue during the study year. It is of note that the residents actually generated a larger amount of collected revenue for private-pay patients since they had an increased number of charges per patient visit.14 Charges for procedures did not differ among the provider group. The number of laboratory and radiology procedures ordered differed between residents and faculty, with residents generating charges of \$12.50 more per visit than faculty due to their increased use of hospital laboratory and radiology services. Since ancillary revenues are not credited to the CMG cost center, they do not contribute to the analysis from the perspective of the physician group. An analysis that measures the total financial impact of the program to the hospital would necessarily need to include laboratory, radiology, and inpatient-related revenues and expenses.

Figure 1 demonstrates that collected revenue per visit is maximized at a level of 5000 visits per year at \$32.60 and plateaus at the 14 000 visits per year level at \$19.23. Figure 2 demonstrates that the expense per visit is greatest at the 5000 visits per year activity level. This expense level of \$57.15 falls off until the practice level reaches 11 000 visits per year. The step function seen in Fig 2 shows an increase to \$39.51 at the 12000 per year visit level since a nurse-practitioner is added and the business manager is made a full-time employee. Little change in expense per visit occurs between the 11000 and 17000 visits per year range once the step function is overcome by the increased activity level.

When expenses are reduced by collected revenue (Fig 3), the least expensive activity level occurs at 11999 visits per year, with each visit costing \$13.14. Activity levels of 13000 and 15000 visits per year are a few cents higher, with a significant change due to the staffing changes required at 12000 visits.

At each activity level, the hospital contributes more to the underwriting

of this practice. Using Medicare cost reports, the hospital's contribution is fixed at \$161 000 plus \$13.88 per visit. At a visit level of 5000 per year the hospital contribution to the practice is \$231000. This increases at a linear rate such that at the 17000 visits per year level it approaches \$400 000. It is difficult to defend the magnitude of the hospital's contribution to the practice since it is historically based on Medicare cost-accounting methods. In 1983, Smith et al¹⁵ described a method for determining the true cost of hospital-based ambulatory care. The CMG-negotiated space rental rate of \$25 per square foot per year may result in more realistic appraisals by the hospital administration of its contribution to the program in future years.

The hospital's contribution to the practice (\$161000 plus \$13.88 per visit) can be divided into two components: one for practice income to the pediatric department and a second to cover the practice deficit. Since the physicians are held fiscally responsible for both collected revenue and practice expenses, only their income can be allowed to vary. As demonstrated in Fig 4 the total hospital contribution always equals the sum of the physician's income and the practice deficit. Physician income plateaus at a level of less than 12000 visits per year at \$169 000. Earnings to the pediatric department are jeopardized by adding more staff and Medicaid patients, and do not increase with increased activity levels. Residents produce little if any income, since they follow up primarily Medicaid-funded patients. Betterpaying patients who have private insurance and the ability to pay noninsured charges show a preference for being seen by the faculty. In addition, a census level of just under 12000 visits per year requires no curtailment of continuity clinic sessions for resident training.

COMMENT

Although the primary purpose of our analysis was to determine the optimal activity level for physician income maximization in a hospitalbased clinic, there are several additional reasons to perform such an analysis. First, the physician group is in a unique position to control the allocation of hospital resources and can greatly influence the ultimate costs of medical care. Hospital-based clinic practices need to integrate physician financial incentives with the programmatic objectives of the hospital. Relatively small changes in income to the clinical department may have major changes in the hospital contribution to the operation of the clinic. Faculty will generally respond to fiscal incentives that link directly to their departmental and personal income. These earnings can provide necessary salary support for the clinical faculty and a means for the ongoing teaching responsibilities of the department. Hospital underwriting of outpatient proshould coincide with encouragement of physician behaviors toward a desired outcome. For example, the effect of the outpatient practice on hospital revenues and expenses in ancillary and inpatient areas might justify changing the financial incentives to the physicians' hospital-based

ambulatory practice.

Second, the analysis presented herein can be used to assist practicing physicians in developing practice policies that encourage improved earnings for their clinical department. Third, costs related to medical education can be isolated if the resident's portion of the practice activity are excluded from the analysis. By determining both the cost to the hospital and the loss of income to the practice physicians, a valid estimate of the costs of operating a teaching program can be made. Finally, the methods of analysis have the potential to serve as a means for educating physicians, residents in training, and other personnel on operating a cost-effective medical practice.

Based on the method of analysis we have described, the optimal financial performance level of the CMG would be achieved at a practice level of just under 12000 visits per year. At this activity level, there would be no decrease in resident experience, the hospital underwriting would be mini-

mized at a level necessary for the existing level of resident training, and the profit (physicians' income) returned to a clinical department would be maximized. An ethical problem from the physician's perspective is created by seeking only profit maximization. To accomplish this end, faculty would have to restrict their personal services to only the better-paying patients. This would favorably alter practice collection rates without increasing the overall practice size above the optimal 11999 visits per year. In this scenario, Medicaid-funded patients would only be seen by residents and the hospital would serve fewer poor children living in the surrounding community. These conclusions are unique to the practice analyzed, since hospital policies on sharing fiscal responsibility with clinical departments vary and reimbursement rates for various payer classes also differ among medical centers. However, the method for performing this analysis is generalizable.

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Indomethacin-Associated Sepsis in Very-Low-Birth-Weight Infants

Victor C. Herson, MD; Peter J. Krause, MD; Leonard I. Eisenfeld, MD; Linda Pontius, MS; Eufronio G. Maderazo, MD

 Indomethacin sodium promotes closure of the patent ductus arteriosus in premature infants. In addition to renal and gastrointestinal side effects, indomethacin may predispose to infection because of inhibition of polymorphonuclear leukocyte (PMN) function. We retrospectively assessed the incidence of sepsis in a group of 58 premature infants with patent ductus arteriosus who received either oral indomethacin, surgery, or usual medical management. A significant increase in the incidence of sepsis was observed in the indomethacin-treated group compared with patients treated with surgery or usual medical management (seven of 31 vs one of 27). All episodes of sepsis occurred within one week of therapy. Patients in the indomethacin group who developed sepsis were less mature, had more gas-

Indomethacin sodium is accepted therapy for closure of a patent ductus arteriosus (PDA) in symptomatic premature infants.¹ Complications of this treatment include oliguria,² transient renal failure, platelet dysfunction,³ gastrointestinal tract hemorrhage, and necrotizing enterocolitis.⁴ Although, to our knowledge, infectious morbidity related to indomethacin therapy in neonates has not been reported, we have been impressed by the close temporal association of in-

trointestinal symptoms, and were less likely to survive than nonseptic indomethacin-treated patients. Nine patients studied prospectively showed no difference in PMN chemotaxis and adherence before and after indomethacin administration. Neither adult nor neonatal cord PMN chemotaxis was inhibited following in vitro incubation with concentrations of indomethacin ranging from 1 to 1000 mg/L. Bactericidal activity of neonatal cord neutrophils was also unaffected by concentrations of indomethacin from 1 to 200 mg/L. These results suggest that oral indomethacin administration may predispose the very-lowbirth-weight infant to the development of sepsis shortly after therapy is begun although the mechanism remains un-

(AJDC 1988;142:555-558)

domethacin therapy and sepsis in our nursery. Indomethacin has anti-inflammatory properties that are due at least in part to inhibition of polymorphonuclear leukocyte (PMN) function. Previous investigators found decreased PMN chemotaxis following indomethacin therapy in experimental Escherichia coli infection in rabbits. In another study, adult PMN intracellular killing was also inhibited by indomethacin.6 These observations prompted this study to determine whether oral indomethacin therapy for neonates with symptomatic PDA predisposes to sepsis, and if so, whether this is due to inhibition of neonatal PMN function by indometh-

PATIENTS AND METHODS Chart Review

All newborn infants admitted to the Neonatal Intensive Care units at Hartford Hospital and the University of Connecticut

Health Center from Jan 1, 1983 through Jan 31, 1984 with a diagnosis of PDA were reviewed. Patients were grouped according to therapy received for their PDA: oral indomethacin, surgical ligation, or usual medical management (neither indomethacin nor surgery). Therapy was individualized by any one of six attending neonatologists. Patients undergoing surgical ligation within one week of indomethacin therapy were excluded from analysis. Sepsis was defined as either (1) a positive blood or cerebrospinal fluid culture, or (2) clinical signs and symptoms of pneumonia and sepsis, evidence of pneumonia on chest roentgenogram, PMNs on Gram's stain of a tracheal aspirate, and pathogenic microorganisms on tracheal aspirate culture. To be considered treatment related, sepsis events had to have occurred within one week following indomethacin administration or surgical ligation. Infants undergoing surgical ligation received cefazolin sodium the day of surgery and for 48 hours afterward as antimicrobial prophylaxis. For infants treated with usual medical management, only episodes of sepsis occurring one week or less after the initial diagnosis of PDA were included in the analysis.

Neutrophil Function Tests

Polymorphonuclear leukocyte chemotaxis and adherence were measured before and two to four hours after indomethacin therapy for closure of PDA in a separate group of nine infants following informed parental consent and in accordance with institutional review board approval. Polymorphonuclear leukocyte motility and bacterial killing following incubation with indomethacin were performed in PMNs from neonatal cord blood or adult volunteers. All tests were run in duplicate or triplicate with simultaneous adult control subjects.

Polymorphonuclear leukocyte motility was measured using a whole blood (Micropore) filter assay⁷ with (chemotaxis) and without (chemokinesis) a chemoattractant

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in the bottom compartment of a modified Boyden chamber. The chemoattractant used was 3% stabilized activated serum prepared by adding zymosan to adult serum (5 mg/mL) in the presence of 1 mol/L of ε-aminocaproic acid, followed by heat inactivation at 56°C for two hours. A PMN suspension (5×105 PMNs in 0.7 mL of Medium 199 [Difco] was allowed to migrate through a 13-mm-diameter, 5-mm-poresized cellulose filter at 37°C in humid air for 90 minutes. Following lysis of erythrocytes with 3% acetic acid, the filters were fixed, stained, and clarified. Polymorphonuclear leukocytes were counted at each 10-µm interval into the filter beginning at 20 µm. The average distance traveled per cell or the locomotion index (LI) was calculated using the following formula: LI = Σ $(N \times D)/\Sigma$ (N), where N is the total number of PMNs counted and D is the distance of the cell from the proximal cell monolayer. Since counting began at 20 µm, this index is called LI20. The filter-to-filter coefficients of variation for adult PMN chemokinesis and chemotaxis in our laboratory were 8.7% and 9.7%, respectively.

Polymorphonuclear leukocyte adherence was assayed with a whole blood, glass coverslip technique.8 A 20-µL drop of chilled blood was placed on a clean glass coverslip and incubated for 45 minutes in a humid 37°C chamber. A clot formed that was carefully removed with forceps, leaving an adherent circle of PMNs. The coverslip was gently rinsed with Medium 199. stained, and mounted on a glass slide. The PMNs were counted along a horizontal and vertical diameter of the circle. The percent of adherence was calculated by the following formula: % PMN adherence = [{(PMNs/area) ×total area of circle counted}/PMNs in original 20-μL blood sample]×100. Slideto-slide coefficient of variation for this assay with adult PMNs was 10.1%. Polymorphonuclear leukocyte killing was assessed using a Staphylococcus aureus quantitative killing assay providing a ratio bacteria per PMN.9 Polymorphonuclear leukocytes isolated from neonatal cord blood of healthy infants were incubated with increasing concentrations of indomethacin from 0 to 200 mg/L. Lysostaphin was used to enumerate phagocytosed bacteria and live intracellular bacteria.9 The PMN bacterial mixtures were sampled at 15, 30, and 60 minutes and plated on agar, and the number of total live intracellular bacteria was determined. Duplicate experiments were done.

Statistical analyses were performed using both paired and nonpaired Student's t test and χ^2 analysis with Yates' correction. Significant differences were considered when P values were less than .05.

| | indomethacin (n = 31) | Ligation (n = 12) | Usual Medical Management (n = 15) |
|---------------------------------|----------------------------|----------------------------|---|
| Birth weight, kg* (range) | 1.07 ± 0.43 (0.60-2.55) | 0.89 ± 0.20 (0.58-1.20) | 1,23 ± 0,37 (0,54-1,85) |
| Gestational age, wk* (range) | 28.5 ± 2.5 (25-31) | 26.9 ± 1.6 (25-30) | 29.9 ± 2.5 (25-34) |
| Age at therapy, d* (range) | 10.6 ± 10.0 (2-52) | 10.9 ± 4.0 (6-18) | ** * ********************************* |
| M/F | 15/16 | 6/6 | 10/5 |
| Respiratory distress syndrome | 25/31 | 10/12 | 11/15 |
| Ventilator | 26/31 | 11/12 | 12/15 |
| Umbilical artery catheter | 14/31 | 6/12 | 12/15 |
| Hyperalimentation | 17/31 | 10/12 | 8/15 |
| Antibiotics† | 11/31 | 12/12 | 7/15 |
| Survival | 26/31 | 10/12 | 14/15 |
| Sepsis‡ | 7/31 | 0/12 | 1/15 |

^{*}Values are mean ± SD

RESULTS Chart Review

Of the 63 patients with PDA reviewed, five were excluded because surgical ligation occurred within one week of indomethacin therapy. The clinical characteristics of the remaining 58 patients divided into the three treatment groups are shown in Table 1. The groups were similar except for the increased antibiotic use in the group that did not receive indomethacin as a result of prophylactic antibiotics for surgery.

Sepsis occurred in seven (22.6%) of 31 infants treated with indomethacin (95% confidence interval, 9.6% to 40.9%) vs one (3.7%) of 27 infants treated with surgery or usual medical management (95% confidence interval, 0.08% to 18%) (P < .05). The clinical characteristics of the seven infants who developed sepsis following indomethacin are shown in Table 2. All patients received two doses of oral indomethacin (0.2 mg/kg) 12 hours apart, with the exception of patient 5 who accidentally received 0.4 mg/kg once. The interval between indomethacin therapy and sepsis ranged from one to six days, with a mean of three days. All infants were bacteremic except patient 3 who had clinical and radiologic evidence of pneumonia and a positive tracheal aspirate culture for Pseudomonas aeruginosa. Infection was at least partially responsible for

death in four of the seven infants who died. Autopsies were performed in two of the four infants who died and both confirmed the presence of infection by culture and histopathologic features.

Analysis of infected infants by calendar month, hospital of origin, and attending neonatologist revealed no clustering of cases in time or place. This suggests that neither a coincidental nursery infectious outbreak nor individual physician practice was responsible for the association of infection with indomethacin.

Among the patients treated with indomethacin, the seven infants who developed sepsis were compared with the 24 infants who remained free of infection. The sepsis group was significantly less mature $(26 \pm 1.4 \text{ weeks vs})$ 29 ± 2.6 weeks [mean \pm SD]; P < .05), less likely to survive (three of seven vs 23 of 24; P < .01), and showed more concomitant gastrointestinal symptoms such as abdominal distention and heme-positive stools (three of six vs two of 24; P < .05) than the noninfected group. The incidence of other clinical characteristics such as respiratory distress syndrome, mechanical ventilation, umbilical artery catheterization, hyperalimentation, antibiotic therapy, PDA closure, and oliguria did not differ between the two groups.

The efficacy of indomethacin therapy is compared with the sepsis com-

[†]Indomethacin vs ligation and expectant, P<.01.

[‡]Indomethacin vs ligation and expectant, P<.05.

Table 2.—Clinical Characteristics of Septic Neonates Who Were Given Indomethacin

| Patient No. | Birth Weight, kg | Gestational Age, wk | Age, d | interval, d | Organism* | Outcome |
|----------------|------------------------|------------------------|-----------|----------------|--------------------------------|----------|
| 1 | 0.9 | 26 | 6 | 6 | Pseudomonas aeruginosa (B) | Died |
| 2 | 1.12 | 29 | 2 | 3 | Staphylococcus aureus (B) | Died |
| 3 | 0.77 | 26 | 6 | 2 | P aeruginosa (TA) | Died |
| 4 | 0.60 | 25 | 7 | 4 | Staphylococcus epidermidis (B) | Died |
| 5 | 0.80 | 27 | 11 | 2 | Klebsiella oxytoca (B) | Survived |
| 6 | 1.10 | 28 | 20 | 1 | S aureus (B) | Survived |
| 7 | 0.74 | 26 | 13 | 2 | S aureus (B) | Survived |

^{*}B indicates blood; TA, tracheal aspirate.

Table 3.—Risk of Sepsis Compared With Patent Ductus Arteriosus Closure Rate in Neonates Treated With Indomethacin

Birth Weight, kg*

<1 ≥1

Sepsis risk 0.31 (0.11-0.58) 0.14 (0.02-0.40)

Patent ductus arteriosus closure 0.50 (0.25-0.75) 0.67 (0.38-0.88)

Risk-benefit

0.6 (0.15-2.32)

plication rate in Table 3. For infants weighing less than 1 kg treated with indomethacin, 31% developed infection while 50% responded with permanent ductal closure. Infants weighing more than 1 kg had a lower infection rate, a higher ductal closure rate, and hence a better risk-benefit ratio.

ratio

In Vivo PMN Studies

There was no significant effect of indomethacin on PMN adherence or chemotaxis in nine infants studied before and after indomethacin treatment. Polymorphonuclear leukocyte chemokinesis and chemotaxis were 34.5 ± 12.7 µm and 41.2 ± 14.2 µm, respectively, prior to indomethacin treatment and $34.5 \pm 13.5 \mu m$ and $43.0 \pm 16.3 \mu m$, respectively, following indomethacin therapy. Mean adult control values for chemokinesis and chemotaxis were $48.2 \pm 20.1 \mu m$ and $50.2 \pm 20.3 \mu m$, respectively. Polymorphonuclear leukocyte adherence values in neonates before and after indomethacin therapy were identical at $0.5\% \pm 0.4\%$. This compared with a mean adult control value 24.8% ± 5.1%.

In Vitro PMN Studies

0.2 (0.02-1.1)

There was no inhibition of chemotaxis of either neonatal cord PMNs or adult PMNs exposed in vitro to increasing concentrations of indomethacin up to 1000 mg/L of PMN. Similarly, the bactericidal and phagocytosis activities of neonatal cord PMNs were unaffected by increasing concentrations of indomethacin up to 200 mg/L of PMNs (data not shown).

COMMENT

The results of this study suggest that oral indomethacin therapy for PDA in low-birth-weight infants may be associated with a significant risk of sepsis (23% [7/31]) compared with the risk in infants treated surgically (0% [0/12]) or managed with usual medical management (7% [1/15]). These results should be interpreted cautiously, however, because of the uncontrolled, retrospective nature of the study and the small sample size. Nevertheless, the close temporal association between indomethacin therapy and the sepsis events favors a cause and effect relationship.

The mechanism for the development of sepsis after indomethacin is unclear.

Polymorphonuclear leukocytes from healthy neonates have decreased adherence^{8,10,11} and chemotaxis^{7,10,12} compared with those of adults while premature stressed neonates have further impairment of chemotaxis13 and decreased bactericidal activity.14,15 An adverse effect of indomethacin on neonatal PMN function might therefore help explain the increased incidence of sepsis in indomethacin-treated neonates. In our study, however, neonates treated with indomethacin showed no change in PMN chemotaxis or adherence during therapy. Neonatal and adult PMN chemotaxis were unaffected by in vitro exposure to increasing concentrations of indomethacin. Additionally, cord PMN bactericidal and phagocytic capacities were unaltered by in vitro incubation with indomethacin. Our data, therefore, do not support the hypothesis that indomethacin-associated sepsis is due to indomethacinrelated PMN dysfunction. This finding differs from the results of Horan et ale who found impaired bactericidal activity of adult PMNs exposed in vitro to indomethacin. Since the methods used were comparable, explanation of the discrepancy is not clear. It is still possible, however, that patients treated with indomethacin may be predisposed to infection by its effect on other cells of the immune system. including macrophages. 16

It may be significant that among our patients treated with indomethacin. gastrointestinal signs and symptoms were seen more frequently in those developing sepsis. Thus, disruption of enteric mucosa may partially explain the sepsis associated with oral indomethacin therapy. Gastrointestinal effects of indomethacin have been previously described and include occult or gross enteric blood loss, abdominal distention with ileus, and frank necrotizing enterocolitis.4 In 1985, Alpan et al17 described four very-low-birthweight infants who developed localized intestinal perforation after oral indomethacin therapy. A direct irritation of mucosa following oral administration may occur. Alternatively, reduction in mesenteric blood flow after indomethacin similar to that which occurs in the kidney18 could explain

^{*}Numbers in parentheses indicate 95% confidence intervals.

these symptoms. Disruption of enteric mucosal integrity could predispose to microbial invasion and bacteremia with or without clinically apparent necrotizing enterocolitis. Of the organisms responsible for the seven cases of indomethacin-associated sepsis in this study, P aeruginosa and Klebsiella oxytoca are common inhabitants of the gastrointestinal flora. Staphylococcus aureus gastrointestinal colonization of the healthy neonate is uncommon but occurs more frequently in the neonatal intensive care unit setting, perhaps in part due to indwelling nasogastric or nasojejunal tubes.19 Furthermore. S aureus septicemia has been reported with necrotizing enterocolitis.20 Therefore, although stool cultures were not obtained in these septic infants, the microbial spectrum seen is not inconsistent with a gastrointestinal source.

The group without indomethacin treatment had a higher incidence of concomitant antibiotic therapy than the indomethacin-treated group primarily because of the use of prophylactic antibiotics for surgical ligation (Table 1). It is unlikely, however, that this was the cause of the decreased rate of sepsis in the group that did not receive indomethacin because (1) the mean duration of antibiotic therapy was only three days compared with a posttreatment period of seven days; (2) the incidence of sepsis among in-

fants receiving antibiotics at the time of the PDA therapy (three of 30) did not differ from patients who were not treated with antibiotics (five of 28, P>.1); and (3) among the 31 infants treated with indomethacin, the frequency of concurrent antibiotics was the same for those developing sepsis (two of seven) as those remaining infection free (nine of 24, P>.1).

The increased incidence of sepsis noted in the indomethacin group in this study was not observed in infants treated with indomethacin in the National Collaborative PDA Study. In the latter study, indomethacin was administered intravenously while the patients in this study were treated with the standard oral preparation. Thus, it is possible that the difference in the incidence of sepsis between the two studies resulted from gastrointestinal side effects of oral indomethacin. Another possible explanation for the difference is the definition of indomethacin-related sepsis in the two studies. For this study, an indomethacin-related septic event was defined as that occurring within one week following therapy, whereas in the Collaborative Study, episodes of sepsis occurring at any time during hospitalization were included. The former criteria may be more specific when examining a potential cause and effect relationship between indomethacin and sepsis.

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The combination of increased morbidity and decreased efficacy of indomethacin in very-low-birth-weight infants with symptomatic PDA makes indomethacin therapy less attractive for this subgroup of infants. The least mature neonates treated with indomethacin in this study were most susceptible to sepsis. All seven episodes of sepsis occurred in neonates weighing less than 1200 g, with five of seven weighing less than 1000 g. The decreased permanent ductal closure rate following indomethacin in the least mature infants is in accord with previous observations.21 The clinician should thus carefully consider the risk-benefit ratio of indomethacin vs surgical therapy for the very-lowbirth-weight infant. Very-low-birthweight infants treated with oral indomethacin may need to be observed closely over the ensuing week for the development of sepsis. These results and conclusions are preliminary. Further prospective studies of sepsis in infants treated with indomethacin will need to be done to confirm these findings.

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Rosario Pock gave technical assistance, and Marie Westlake assisted in preparation of the manuscript.

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Bacteremia With Group A Streptococci in Childhood

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 Medical records of 60 patients with bacteremia caused by group A streptococci who were treated at the Yale-New Haven (Conn) Hospital from 1973 to 1986 and the Boston Children's Hospital Medical Center from 1977 to 1984 were reviewed. Seven children (12%) were immunocompromised, seven (12%) had varicella, and two (3%) had cavernous hemangiomas. Fifty-two children (87%) had an identifiable focus of infection. The most commonly documented sources of bacteremia were in the skin (22 children) and the respiratory tract (19 children). Metastatic foci of infection included osteomyelitis (nine children). septic arthritis (eight children), and men-Ingitis (three children). Seven episodes were nosocomial (four were catheter related and three occurred postoperatively). Four patients (7%) died: two were severely immunocompromised, one of whom had extensive hemorrhagic varicella; the third had widespread hemorrhage into a large cavernous hemangioma of the skin; the fourth had an initial diagnosis of sudden infant death syndrome. Bacteremia with group A streptococci, although uncommon, continues to cause serious infections in children during the antibiotic era.

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Group A streptococci (GAS) are a common cause of pharyngitis and skin infections in children. Lifethreatening suppurative complications

See also p 562.

have been reported in some series of immunocompromised children and in others without underlying disease.¹⁻⁵

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Reprints not available.

The recent development of rapid diagnostic tests and the resurgence of acute rheumatic fever^{8,7} have generated renewed interest in this organism and its expanded clinical spectrum. We present a retrospective review of an unselected series of children with GAS bacteremia, generally considered a rare clinical entity since the advent of the antibiotic era.⁸

PATIENTS AND METHODS

The medical records were reviewed of children younger than 18 years of age who had GAS isolated from at least one blood culture from July 1973 to June 1986 in the bacteriology laboratories of the Yale-New Haven (Conn) Hospital and from January 1977 to December 1984 at the Children's Hospital of Boston. From 1973 to 1980 at Yale-New Haven Hospital and from 1977 to 1980 at the Children's Hospital of Boston, isolates of streptococci were identified presumptively at GAS by \(\beta\)-hemolysis on blood agar and susceptibility to bacitracin with negative results of hippurate and bile esculin tests. In addition, at the Children's Hospital of Boston, the isolates were further confirmed as GAS with specific sera for typing (Burroughs Wellcome, Dartford, England). Since 1981 at both hospitals, definitive identification of isolates was conducted by demonstrating their resistance to the combination of trimethoprim and sulfamethoxazole9 and by confirming their identity with a rapid latex agglutination test (Streptex, Wellcome Diagnostics, Dartford, England).

Infections were defined as nosocomial if the first positive blood culture was obtained after an elective hospital procedure or after four days of hospitalization without clinical evidence of infection at the time of admission. Infections determined by a culture of the intravenous catheter site positive for GAS and accompanied by clinical signs of cellulitis or phlebitis and the isolation of GAS from blood drawn through the intravenous line were also considered to be nosocomial.

Primary foci of infection were defined as those sites at which there was inflammation or purulent drainage that historically antedated the bacteremia. Infected sites that became apparent only after the bacteremia was established were defined as metastatic foci of infection. Meningitis and infections of the bones and joints were considered metastatic sites of infection in the absence of coexistent foci in the skin or respiratory tract

RESULTS

Sixty-two patients with GAS bacteremia were documented (37 patients from Yale-New Haven Hospital encountered during a 13-year period and 25 patients from the Boston Children's Hospital encountered during an eight-year period). Charts could not be located for two of these patients, an 8-year-old child with acute leukemia who died and a 1-year-old child who was successfully treated as an outpatient. The remaining 60 patients form the basis of this report.

Patient ages ranged from 1 day to 18 years, with a median age of 4 years. There were 35 boys and 25 girls. Fifty-four children were hospitalized and six were treated as outpatients. There was no significant seasonal variation in the frequency of these episodes.

Clinical Presentation

The clinical signs and symptoms were generally related to the focus of infection. Fifty-two patients (87%) had at least one identifiable focus of infection, with 22 having two or more foci. A primary focus of infection was identified in 41 patients (68%). A metastatic focus from hematogenous dissemination was present in 24 patients (40%). Only seven patients (12%) were immunocompromised, including one patient each with neuroblastoma, non-Hodgkin's lymphoma, leukemia, severe malnutrition, protein-losing enteropathy, galactosemia, and severe combined immunodeficiency.

Forty-three patients (72%) had a recorded temperature of greater than 38.5°C; one neonate was hypothermic. Thirty-nine patients (65%)

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| Foci I | No. of Patients |
|---------------------------|--------------------|
| Primary | |
| Respiratory tract | |
| Pharyngitis | 11 |
| Pneumonia | 8 |
| Sinusitis | 6 |
| Otitis media | 5 |
| Other | 5 |
| Skin | |
| Varicella | 7 |
| Cellulitis | 5 |
| Wound infection | 4 |
| Abscess | 3 |
| Intravenous catheter site | 3 |
| Other | 5 |
| Metastatic | |
| Osteomyelitis | 9 |
| Septic arthritis | 8 |
| Pneumonia | 4 |
| Meningitis | 3 |
| Peritonitis | 2 |
| Subdural empyema | 1 |
| Flank hematoma | 1 |
| Other | 3 |

*Some children had more than one focus of infection.

had a white blood cell count of greater than $12 \times 10^8/L$ (> $12 \times 10^8/mm^8$) and three (5%) had less than $1 \times 10^6/L$ (< $1 \times 10^8/mm^8$). Two children had polymicrobial septicemia with Staphylococcus aureus as well as GAS, one of whom was a severely immunocompromised neonate. The clinical foci of infection are shown in the Table.

Respiratory Tract Infections

Twenty-five patients (42%) had at least one focus of infection in the respiratory tract. In 19 children the respiratory tract was the primary source of bacteremia. Pneumonia and pharyngitis occurred most frequently, accounting for 12 and 11 episodes, respectively. Group A streptococci were isolated from the pharynx in the seven children with pharyngitis in whom throat cultures were performed. The onset of pneumonia was preceded by varicella in three children. Radiographic findings in 11 children with pulmonary involvement included unilateral (seven children) and bilateral (four children) infiltrates, with lobar (seven children), segmental (three children), and interstitial (one child) distribution. One child had roentgenographic evidence of pericardial and pleural empyemas from which GAS were isolated. Other foci included sinusitis, otitis media, and cervical adenitis.

Skin Infections

The skin was the primary site of infection in 22 children (37%), ten of whom subsequently developed a metastatic focus of infection. All had antecedent skin lesions that were the presumed portal of entry into the blood stream for the streptococci. The GAS bacteremia associated with extensive varicella accounted for seven of the episodes, three of which were associated with cellulitis. One patient had severe hemorrhagic varicella and another had extensive gangrene. Other skin infections included infected intravenous catheter sites, intertrigo, erysipelas, postoperative wound infections, eczema, and cavernous hemangiomas.

Musculoskeletal Infections

Complications from hematogenous dissemination of GAS were noted in 14 patients (23%) who developed musculoskeletal infections; six children had osteomyelitis, five had septic arthritis, and three had both. All were proved roentgenographically and/or by isolation of GAS from a bone or a joint. Multifocal involvement was noted in three patients with osteomyelitis and one with septic arthritis. Five of the eight patients had osteomyelitis involving long bones.

Other Foci of Infection

Other foci of infection included meningitis (three patients), peritonitis (two patients), subdural empyema (one patient), flank hematoma (one patient), and terminal ileitis (one patient). Six cases of bacteremia had no apparent focus of infection.

Nosocomial Infections

Seven (12%) of the episodes were nosocomial. Four immunocompromised patients with intravenous catheters (Broviac [two patients] and peripheral [two patients]) developed nosocomial bacteremia, one of whom had an abscess at the site of catheter insertion. Three patients became bacteremic on their first postoperative day: one had a coexistent wound infection with GAS, and the others became bacteremic after repair of a cleft palate and a dental procedure, respectively.

Outcome

Most of the infections responded promptly to treatment with penicillin. Sixteen children had more than two days of fever in the hospital while receiving appropriate antimicrobial agents, eight of whom required surgical drainage of a purulent focus of infection and defervesced immediately after surgery (although in the five in whom drainage was delayed beyond four days, all remained febrile until the time of drainage). In the remaining eight children who did not have a purulent focus of infection, the patients defervesced within four days of the initiation of antibiotic therapy. Five children did not receive antibiotics: three had occult bacteremia, one had a respiratory focus, and the other had terminal ileitis with peritonitis and underwent an appendectomy. All of these children recovered without sequelae.

One child developed erythema nodosum and glomerulonephritis, and another had scarlet fever. Other complications included disseminated intravascular coagulation (four patients), septic shock (three patients), acute renal failure (two patients), cerebrovascular accident (one patient), coma (one patient), and hemiparesis (one patient).

Four patients died, including a male neonate with combined immunodeficiency, zinc deficiency, severe eczema, and recurrent skin infections, who presented with septic shock and had coexistent polymicrobial peritonitis; an 18-year-old boy with protein-losing enteropathy and hemorrhagic varicella who developed widespread pulmonary consolidation with respiratory failure as well as septic shock; a 5-yearold boy with extensive hemorrhage into a large cavernous hemangioma of the skin, who developed extensive pneumonia, septic shock, renal failure, and disseminated intravascular coagulation; and a 6-month-old female infant whose initial diagnosis was sudden infant death syndrome.

COMMENT

Bacteremia with GAS has been relatively rare in children since the advent of the penicillin era.^{8,10} Despite active nationwide solicitation, a British ref-

erence laboratory received only 64 blood isolates from adults and children over a three-year period."

Only 12% of the children in this series were immunocompromised, in contrast with the high frequency of this association noted in previous reports. 1.12-16 The association of GAS bacteremia with lymphoreticular malignant neoplasm, cavernous hemangiomas, galactosemia, and solid tumors has been documented previously. 1.2.5,14,17

Eighty-seven percent of our patients had a recognized focus of infection, in contrast to 38% in the classic series of Keefer and colleagues¹⁸ in the preantibiotic era that described 246 adults and children.¹⁸ The association between GAS bacteremia and pharyngitis is unusual¹⁹ and only has been documented for immunocompromised

children.^{1,18,18} However, we found that 16% of the children in this series had pharyngitis.

Group A streptococcal pneumonia is rare, accounting for 1.3% of positive bacterial isolates in 530 cases of childhood pneumonia diagnosed by lung puncture.20 The association with varicella, the complicated clinical course, and the high mortality rate are similar to other reports of GAS pneumonia.2,4,21-27 Empyema developed in only one of 12 patients in this series, compared with 66% to 100% of adults and children with GAS pneumonia in other reports. 2,4,22,27,28 Interstitial bronchopneumonia is the most common form and had a 75% incidence in a series of children,4 in contrast to this report in which pneumonia with lobar or segmental distribution occurred more frequently. Endocarditis, a complication in adults, was not observed in our series.14

All children with a focus of infection in the skin had preceding skin lesions that became superinfected with GAS. Most had varicella (one developed gangrene that has been reported at the site of GAS invasion). 17,29,30 In the child who appears septic and has inflammatory changes within a skin lesion or postoperative wound, the physician should suspect GAS sepsis.

The overall mortality rate was 7%. Of those who died, two had a fulminant course after extensive hemorrhage into skin lesions. Group A streptococcal bacteremia must be treated aggressively in the hope of preventing metastatic infections and other complications.

We are grateful to Kenneth McIntosh, MD, and Robert Baltimore, MD, for their assistance.

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The Group A Streptococcal Carrier State

A Reexamination

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 Streptococcal infection usually is defined as a positive throat culture with a serologic response to group A β-hemolytic streptococci, and a patient with a positive throat culture and no serologic response is a streptococcal carrier. Studies suggest that streptococcal carriers should show little clinical response to antibiotic therapy when compared with patients with true streptococcal infections. Patients with acute pharyngitis were divided into three groups: group 1-38 patiets with negative throat cultures; group 2-72 patients with a positive throat culture and a significant rise in streptococcal antibody titers; and group 3-77 patients with positive throat cultures and no significant rise in streptococcal antibody titers. Patients in group 2 and group 3 had a comparable and dramatic clinical response to antibiotic therapy that was considerably greater than the clinical response in the patients in group 1. These findings raise questions about the appropriateness of using streptococcal antibody responses to distinguish between the streptococcal carrier state and a true streptococcal infection.

(AJDC 1988;142:562-565)

It is generally believed that many children with group A β -hemolytic streptococci (GABHS) in their upper respiratory tract are streptococcal carriers. However, there is a great deal of confusion regarding the appropriate definition of the streptococcal carrier state and a true streptococcal infection. Much of this confusion has arisen from earlier attempts to define

streptococcal carriage on the basis of culture results and clinical findings alone. 4.5 While most asymptomatic patients with positive throat cultures for GABHS are streptococcal carriers, Gordis and coworkers clearly have demonstrated that some asymptomatic patients have bona fide streptococcal infections and may subsequently develop acute rheumatic fever.

See also p 559.

Conversely, some symptomatic patients with positive throat cultures for GABHS are streptococcal carriers, and their clinical findings presumably are due to an intercurrent upper respiratory tract infection with some other organism.³ Therefore, culture results and clinical findings alone cannot accurately distinguish between the streptococcal carrier state and true streptococcal infections.

A true streptococcal infection usually is defined as a positive throat culture and a serologic response to GABHS, and a patient with a positive throat culture and no serologic response is a streptococcal carrier.1,7 Using these definitions, approximately half of the children in a relatively unselected group of patients with acute pharyngitis and a positive throat culture for GABHS were demonstrated to be streptococcal carriers.3 While completing a recent investigation involving a highly selected group of patients with acute pharyngitis and a positive throat culture for GABHS, we were surprised to find that approximately the same percentage of patients (61%) were carriers.8 We performed cultures in only those patients who were acutely ill and who had clinical findings suggestive of GABHS pharyngitis. Consequently, 75% of our patients had positive throat cultures, and of the patients with positive throat cultures, 100% were febrile and 80% had cervical lymphadenitis. Yet, despite this high degree of selectivity, about half of these patients appeared to be streptococcal carriers as defined above. These observations led us to question the validity of this definition and to examine this issue further.

We and others8,9 have demonstrated previously that children with pharyngitis and a positive throat culture for GABHS have a dramatic clinical response to antibiotic therapy. In contrast, children with pharyngitis and a negative throat culture for GABHS show little clinical response to antibiotic therapy. If children with pharyngitis, a positive throat culture for GABHS but no serologic response to GABHS, are streptococcal carriers and infected with another organism, then it would follow that these children should show little clinical response to antibiotic therapy when compared with children with true streptococcal infections.

A prospective investigation of children with acute pharyngitis was undertaken to test this hypothesis and the validity of the current definition of a streptococcal carrier.

PATIENTS AND METHODS

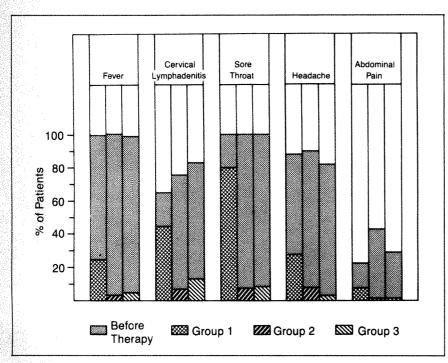
During the winter-spring of 1984-1985, 187 patients with acute pharyngitis seen in a private pediatric office (M.F.R.) were enrolled in the investigation after written informed consent had been obtained. Children who had received antibiotic therapy within the previous 72 hours were excluded.

All study patients were evaluated for the presence and severity of two objective signs

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Percentage of patients in each of three groups with specific clinical signs and symptoms before (upper bar) and after (lower bar) 24 hours of therapy. See text for explanation of groups.

(fever and cervical lymphadenitis, as manifested by tender, enlarged lymph nodes) and three subjective symptoms (sore throat, headache, and abdominal pain) by one of us (M.F.R.). A throat culture was then performed in each patient by vigorously swabbing the posterior pharynx and tonsils (or tonsillar fossae) with a rayontipped swab (Culturette, Marion Scientific, Kansas City, Mo). The swab was then immediately streaked onto a blood agar plate (trypticase soy agar with 10% sheep's blood, BBL Microbiology Systems, Cockeysville, Md), a bacitracin disk (Taxo A Disc, BBL Microbiology Systems) was applied, and the plate was incubated at 37°C for 18 to 24 hours. β-Hemolytic streptococci were presumptively identified as group A or non-group A on the basis of bacitracin sensitivity. Grouping was later confirmed by the Streptex test (Wellcome Reagents, Dartford, England).

All patients were randomly assigned to receive either penicillin V potassium (250 mg per 5 mL) or cefadroxil (250 mg per 5 mL) as part of other investigations. ^{10,11} Parents were instructed to give their child one teaspoon three times over the next 18 to 24 hours if assigned to the penicillin group or 30 mg/kg as a single dose if assigned to the cefadroxil group. They also were instructed to take their child's temperature every four hours during waking hours to note the rate of improvement in the child's clinical status and to

return in 18 to 24 hours with the medicine bottle they had been given. Parents were requested not to administer aspirin or acetaminophen during the study period.

At the 18- to 24-hour follow-up visits, all children were reevaluated by the same physician who had performed the initial assessment and who was unaware of throat culture results or the treatment regimen received. Temperatures were taken, an interim history was obtained, and a physical examination was performed. For each of the predetermined clinical signs and symptoms, the physician determined whether the patient's condition improved, worsened, or did not change. In addition, the physician, parent, and patient (if old enough) were each asked to record their general impressions as to whether the clinical status had shown significant improvement over the preceding 18 to 24 hours. Compliance was determined by history and measurement of unused drug.

The results of the throat culture were then determined. The patients with a throat culture positive for GABHS were instructed to continue the assigned antibiotic regimen for a full ten-day course, while patients with a negative throat culture (group 1) had the antibiotic therapy discontinued at the 18- to 24-hour follow-up visit. All patients with a positive throat culture had a blood specimen drawn at the 18- to 24-hour follow-up visit and were instructed

to return in four weeks, at which time convalescent blood specimens were obtained. All serum specimens were stored at -70°C and later analyzed simultaneously in pairs for antistreptolysin O (ASO) and antideoxyribonuclease B (ADB) titers according to established methods. 12,18 Patients with a positive throat culture for GABHS and a significant rise of two or more dilutions (≥0.2 log rise) in ASO or ADB titers were considered to have true streptococcal infections (group 2), whereas patients with a positive throat culture for GABHS without a significant rise in ASO or ADB titers were considered streptococcal carriers (group 3).

Data were analyzed using the χ^2 test and Student's t test.

RESULTS

Study patients ranged in age from 2 to 25 years (mean age, 10.0 years). Of the 187 patients in whom cultures were performed, GABHS were isolated from 149 (80%). Group 1 comprised the 38 patients (20%) who had negative throat cultures. Of the 149 patients with positive throat cultures. 72 (48%) had a significant rise in ASO or ADB titers and were considered to have true streptococcal infections (group 2); 20 (28%) had a rise in ASO titer only, 20 (28%) had a rise in ADB titer only, and 32 (44%) had a rise in both ASO and ADB titers. The 77 patients (52%) with positive throat cultures who did not have a significant rise in ASO or ADB titers were considered streptococcal carriers (group 3). The patients in groups 1, 2, and 3 were comparable with respect to sex, duration of illness before initiation of treatment, and clinical findings at the initial visit (Figure). The patients with positive throat cultures for GABHS (groups 2 and 3) were comparable in age but were significantly younger (P<.01) than the patients with negative throat cultures (group 1). The distribution of antibiotic therapy and compliance was comparable for the patients in group 2 and group 3, but patients in group 1 did not receive antibiotic therapy.

All 149 children with positive throat cultures returned for the 18- to 24-hour follow-up evaluation. At that time, there was a significant (P<.01) reduction in the number of patients in both group 2 and group 3 who had each of the two objective signs and

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each of three subjective symptoms (Figure). In addition, the evaluating physician, parents, and patients all had the general impression at the 18to 24-hour follow-up evaluation that 92% of the patients in group 2 and 91% of the patients in group 3 exhibited overall clinical improvement. In contrast, there was a significant (P < .01)reduction in the number of patients in group 1 who had one of the two objective signs (fever) and two of the three subjective symptoms (sore throat and headache) at the 18- to 24-hour followup evaluation. In addition, the clinical response to antibiotic therapy for the patients in group 1 was considerably less dramatic than for the patients in group 2 and group 3 (Figure). Furthermore, the evaluating physician, parents, and patients all had the general impression at the 18- to 24-hour follow-up evaluation that only 32% of the patients in group 1 exhibited overall clinical improvement.

COMMENT

Distinguishing between someone with acute pharyngitis who has a bona fide streptococcal infection and someone with acute pharyngitis who is a streptococcal carrier has important clinical implications. Patients with true streptococcal infections are at risk for developing suppurative (eg, peritonsillar abscess) and nonsuppurative (eg, acute rheumatic fever) complications, as well as for transmitting the GABHS to others.1 Therefore, patients with true streptococcal infections should be treated with an appropriate antibiotic. In contrast, patients who are streptococcal carriers are not at risk for developing either suppurative or nonsuppurative complications, and they rarely transmit the GABHS to others.1 Therefore, streptococcal carriers do not need to be treated with antibiotics.

A streptococcal carrier is usually defined as a patient with a throat culture positive for GABHS but with no evidence of an antibody response to that organism, while a true streptococcal infection is defined as a positive throat culture for GABHS and an antibody response. 1.7 Because serologic responses to GABHS may take several weeks to develop, antibody

titers can be used only retrospectively to distinguish between carriers and those who are truly infected. Although numerous attempts have been made to correlate streptococcal antibody responses with clinical findings,³ acutephase reactants,¹⁴ and the degree of positivity of the throat culture,¹⁵ all of these attempts have been unsuccessful. Therefore, there is no accurate way to make this distinction at the time of the initial presentation.

One of the problems with using an antibody response to retrospectively categorize patients as either truly infected or carriers is that virtually all of the patients with pharyngitis and a positive throat culture for GABHS will have received antibiotic therapy. Kaplan and coworkers3 found that 45% of 133 patients with GABHS pharyngitis who were treated with antibiotics had a significant ASO or ADB titer rise, compared with 38% of 34 such patients not treated with antibiotics (P>.05). These findings suggest that antibiotic therapy does not interfere with the streptococcal antibody response. In contrast, several other investigations¹⁶⁻¹⁹ have demonstrated that antibiotic therapy significantly reduces both the magnitude of the ASO and ADB titer responses as well as the number of significant increases in these antibody titers. In addition, these studies showed that the earlier in the course of the pharyngitis antibiotic therapy was initiated, the greater the inhibition of the streptococcal antibody response. Ethical considerations would preclude the performance of an investigation in which streptococcal antibody titers were measured in patients with GABHS pharyngitis while antibiotic therapy was withheld, and this controversy probably will never be resolved completely.

While children with pharyngitis and a positive throat culture for GABHS show a dramatic clinical response to antibiotic therapy, children with pharyngitis and a negative throat culture show little clinical response to antibiotic therapy. 8.9 Because the clinical pharyngitis in patients who are streptococcal carriers presumably is caused by the same agents that produce the clinical pharyngitis in patients with a

negative throat culture for GABHS, one would expect little clinical response to antibiotic therapy in streptococcal carriers. In this study, however, the clinical response to antibiotic therapy in the patients with a positive throat culture and no antibody response to GABHS (group 3) was comparable with the clinical response in patients with a positive throat culture and an antibody response to GABHS (group 2). In addition, the clinical response to antibiotic therapy in both groups of patients with a positive throat culture for GABHS (groups 2 and 3) was considerably greater than the clinical response in patients with a negative throat culture (group 1).

These findings, therefore, raise questions about the appropriateness of using streptococcal antibody responses to distinguish between streptococcal carriers and patients with true streptococcal infections. Furthermore, they suggest that many of the patients who would have been classified as streptococcal carriers using these criteria may have bona fide streptococcal infections. A possible explanation for these findings is that the streptococcal antibody response in many of these patients was inhibited by the use of antibiotic therapy.

The use of streptococcal antibody responses to distinguish between streptococcal carriers and patients with true streptococcal infections is unsatisfactory not only because the information can only be used retrospectively but also because the resulting classifications may not be accurate. Further investigations to better define the streptococcal carrier state and true streptococcal infections are clearly needed.

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In Other AMA Journals

JAMA

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Animals in Research

S. J. Smith, W. R. Hendee (JAMA 1988;259:2007-2008)

Is Pinworm a Vanishing Infection?

Laboratory Surveillance in a New York City Medical Center From 1971 to 1986

Sten H. Vermund, MD, MSc, Sheila MacLeod, MPH

· Records of our parasitology laboratory were reviewed to determine trends in the frequency of specimens submitted for diagnosis of pinworm infection, the proportion of such specimens that were positive, and the proportion of such positive results for the pediatric age group from 1971 to 1986 in a major New York City medical center. These data demonstrate a markedly declining trend in the absolute number of sticky tape tests sent for pinworm diagnosis, from 248 in 1971 to 38 in 1986, an average of 8% decline per year. The number of specimens identifying Enterobius vermicularis among those submitted has similarly declined, from 57 in 1971 to none being positive in 1986, an average of 16% decline per year. The dramatic decline in pinworm identification and the fall in the number of specimens sent by practitioners at this medical center, and reported elsewhere in the United States by other investigators, may reflect a genuine decline in oxyuriasis occurring in the patient populations

(AJDC 1988;142:566-568)

Pinworm has been reported to be among the most prevalent nematodes both in North America and worldwide, 10 with an estimated 42 million cases in the United States in 1972. We suspected, on clinical observation, that oxyuriasis was rare in our population, despite the known prevalence of other parasites. Few surveys of Enterobius vermicularis

prevalence in the United States and Canada have been reported since 1970. 12-15 We reviewed the records of our parasitology laboratory for pinworm identification and also determined the annual number of clinical visits for the period 1971 to 1986 at the Columbia-Presbyterian Medical Center (CPMC), New York.

METHODS

Sticky tape tests were obtained by practitioners or by parents during the interval studies. Presumably, proper techniques of specimen gathering were not always used, but this phenomenon should have been uniform during the 16 years. No research protocol for the diagnosis of pinworm was in place. Physicians, physicians' assistants, and nurse practitioners almost invariably sent sticky tape tests to the laboratory for confirmation, once collected, even if they first examined the slides themselves in the clinic. The same parasitology technician has been employed from 1968 to the present; sticky tape tests were examined first under direct low-power microscopy (X40), then under high power for confirmation. Laboratory records from 1971 through 1986 were reviewed by us to enumerate all sticky tape tests sent for pinworm diagnosis and all positive tests. We determined the proportion of tests positive over time or the "pinworm positivity rate." We deleted redundant positives, eg, three positive sticky tape tests in the same person in the same time period were counted as a single infection. We used birth dates to identify pediatric patients and determined age-stratified ratios. We performed regression analysis to test for the significance of trends over time.

RESULTS

The frequency of diagnosis of laboratory-confirmed pinworm infection has fallen steadily from 48 persons

with positive test results among 400770 clinic visits in 1971 to none among 471 480 clinic visits in 1986 (Fig 1 and Table). Fewer specimens are being submitted to the laboratory, on average an 8.0% decline per year. The average decline in the proportion of positive tests detected was 8.9% per year (for log. [positive tests/total tests] vs time, $\beta = -0.011$, P < .001) (Fig 2). For example, fully 23.0% of 248 specimens sent in 1971 were positive for E vermicularis eggs, while only 4.9% of 61 specimens sent in 1984 and zero of 38 specimens sent in 1986 were positive. In this 16-year period, 83.2% of all persons with positive specimens were under age 17 years. The frequency of laboratory-confirmed pinworm in the 0- to 16-year age group has fallen from 40 among 54727 pediatric clinic visits in 1971 to none among 92 137 pediatric clinic visits in 1986. The proportion of pediatric patients to the total has decreased markedly (Fig 2); 88.0% of persons with positive test results were under age 17 years in the 1971-1974 time period. This proportion has fallen to 80.6% in the 1975-1978 time period, to 76.9% in the 1979-1982 time period, and to 44.4% in the 1983-1986 time period.

COMMENT

Surveillance data suffer from underreporting, yet trends may be demonstrated for infectious diseases if reporting bias does not differ from year to year. 16,17 The dramatic decline in frequency of pinworm diagnosis demonstrated in the present study at a single institution in New York City has several plausible explanations.

First, since education on parasitic diseases is often limited in many med-

New York (Dr Vermund and Ms MacLeod). Reprints not available.

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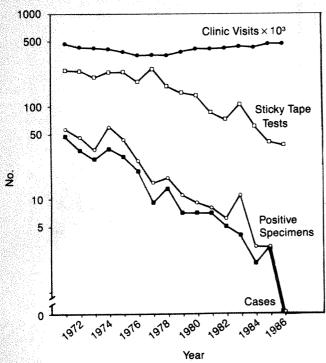


Fig 1.—Total number of sticky tape tests sent to Columbia-Presbyterian Medical Center (CPMC) laboratory (New York), with number of positive specimens and number of persons with *Enter*objus vermicularis infection from 1971 to 1986 at CPMC.

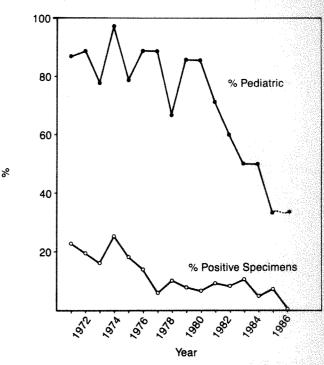


Fig 2.—Percent of persons with positive specimens who were under 17 years of age and percent of total specimens that are positive for *Enterobius vermicularis* per year. Asterisk indicates proportion is without definition as there were no specimens positive for *E vermicularis* in 1986.

ical school curricula, failure to order diagnostic tests for pinworm infection might be attributable to lack of knowledge of the physician. However, this phenomenon would not account for the fall in the proportion of positive tests over the same time period (Fig 2) unless there has been a drastic shift in clinical criteria for obtaining a test or unless a genuine decline in pinworm prevalence had occurred. The likelihood of pediatricians at CPMC neglecting parasitic infections more now than in the past is improbable, based on continuing emphasis in the curriculum and clinical practice that includes awareness of pinworm disease.

Second, the majority of infected individuals are asymptomatic and the decrease in pinworm frequency in recent years could mean that fewer patients are presenting to the clinic for diagnosis of their infection. We believe this is unlikely since there is no evidence that the proportion of symptomatic individuals has declined, and our Parasitologic Data for Enterobius vermicularis Infection at the Columbia-Presbyterian Medical Center in New York City, and Data for Total Clinic Visits From 1971 to 1986

| Year | No. of Sticky Tape Tests Sent | No. of Positive Specimens | No. of Persons With Positive Results* | No. of Pediatric Persons With Positive Results* | Total No. of Clinic Visits† | Total No. of Pediatric Clinic Visits† |
|-------|-------------------------------------|---------------------------------|--|---|--------------------------------------|---|
| 1971 | 248 | 57 | 48 | 40 | 401 000 | 55 000 |
| 1972 | 240 | 47 | 34 | 30 | 433 000 | 62 000 |
| 1973 | 209 | 34 | 27 | 21 | 425 000 | 62 000 |
| 1974 | 235 | 60 | 35 | 34 | 419 000 | 63 000 |
| 1975 | 239 | 44 | 29 | 22 | 381 000 | 61 000 |
| 1976 | 185 | 26 | 20 | 16 | 351 000 | 56 000 |
| 1977 | 252 | 15 | 9 | 8 | 359 000 | 58 000 |
| 1978 | 165 | 17 | 13 | 8 | 358 000 | 61 000 |
| 1979 | 140 | 11 | 7 | 6 | 387 000 | 69 000 |
| 1980 | 132 | 9 | 7 | 6 | 414 000 | 78 000 |
| 1981 | 86 | 8 | 7 | 5 | 416 000 | 76 000 |
| 1982 | 72 | 6 | . 5 | 3 | 423 000 | 82 000 |
| 1983 | 105 | 11 | 4 | 2 | 444 000 | 83 000 |
| 1984 | 61 | 3 | 2 | .1 | 431 000 | 88 000 |
| 1985 | 41 | 3 | 3 | 1 | 472 000 | 90 000 |
| 1986 | 38 | 0 | 0 | 0 | 471 000 | 92 000 |
| Total | 2448 | 351 | 250 | 203 | 6 585 000 | 1 135 000 |

^{*}Eliminating redundant positive results in the same person.

[†]Apparent discrepancy in total due to rounding of all numbers to the nearest thousand

volume of patients has not decreased (Table).

Third, changes in patient characteristics over the 16-year period may account for the decrease in pinworm infections. Since pinworm infection has been found to be twice as high in whites as in blacks and Puerto Ricans in New York18 and other areas, a decrease in the white population presenting to the clinic might explain the lower incidence of this infection in present years. While detailed socioeconomic data in the patients are not available, census data show no apparent changes in the ethnic background of the local population. Also, the proportion of pediatric clinic patients and their absolute numbers have increased since 1970 (Table). The decline, in addition, has occurred concurrent with an increased number of children attending day-care centers, which presumably facilitates spread of enteric pathogens, including E vermicula $ris.^{19-21}$

Fourth, the results may reflect a

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natural variation in pinworm frequency over the study period.12 This explanation is not likely given the steady fall in the proportion of specimens positive, the number of specimens sent, the proportion of persons in the pediatric age group with positive test results, and the absolute number of infections. No instances of E vermicularis infection were diagnosed in 1986.

Finally, the data may reflect a genuine decline in pinworm incidence and prevalence in this population. We believe this to be the most plausible explanation of the data. Sticky tape tests have been performed at our clinic for complaints of anal pruritus or because of suspicion of exposure. It is possible that the relatively benign medication regimen^{9,22-26} may influence practitioners to treat without laboratory confirmation of infection, leading to a reduction in parasitism in the population, as well as fewer tests submitted.

The outpatient pool of CPMC con-

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sists of inner-city families of black and Hispanic (especially Dominican) background, and thus our observations may not be generalizable to other populations. However, an apparent decline in southern California schoolchildren from the early 1960s to the early 1980s has been noted.12 A marked decline in pinworm diagnostic tests in the Kaiser Foundation Health Plan Regional Laboratories, serving a 1.75 million patient pool of predominantly middle/ working class subscribers in northern California, has also been noted (Edward K. Markell, PhD, MD, written communication, Aug 10, 1987). Further studies, in similar and differing populations, should elucidate the current epidemiology of pinworm infection.

John Ma performed the parasitologic work and kept careful records. Francois LaFleur, MPH, a participant in the Health Research Training Program of New York City Department of Health, and Jesus A. Cambrelen, Jr, MPH, aided in data collection. Michael Katz, MD, MS, and Edward K. Markell, PhD. MD. reviewed the manuscript.

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Jaundice in Neonates With Sickle Cell Disease

A Case-Control Study

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• This matched, case-control study was conducted on 68 neonates with sickle cell disease (SCD) to test the hypothesis that SCD contributes to neonatal jaundice. Previous uncontrolled studies have suggested that SCD leads to a high rate of neonatal jaundice. After matching, two neonates without SCD born in the same year were selected for each patient with SCD by use of random numbers. Matching factors were gestational age, sex, birth weight, and race. Serum bilirubin concentrations and the presence or absence of clinical jaundice were recorded. Information on factors potentially influencing the rate of neonatal jaundice was obtained for the first three days of life: maternal drug, alcohol, and tobacco usage, intrauterine infection, Apgar scores, highest infant hematocrit, culture-proved sepsis, blood group incompatibilities, hemorrhages, and presence of red blood cell sickling. We found no increase in the rate of clinical jaundice and no increase in the bilirubin concentration in either the entire group of patients with SCD, or in the subgroups with either homozygous or S-hemoglobin C disease, compared with their respective controls. We conclude that SCD probably is not a significant factor predisposing to neonatal jaun-

(AJDC 1988;148:569-572)

In sickle cell disease (SCD), the coexistence of red blood cell sickling and jaundice has been reported in the newborn period.1-10 Therefore, several investigators have suggested that an association exists between SCD and neonatal jaundice. 3,5-11 These reports examined small numbers of patients, did not compare patients with normal control subjects, and failed to examine several factors that may affect neonatal bilirubin concentration. In this case-control study, we tested the hypothesis that infants with SCD have a higher rate of neonatal jaundice and higher serum bilirubin concentrations than pair-matched normal controls.

PATIENTS AND METHODS

A cord-blood screening program for the detection of hemoglobinopathies was implemented in Cincinnati in June 1974. The hemoglobin electrophoresis pattern of all newborns was determined first on cellulose acetate plates12 and was repeated using citrate agar plates if abnormal.13 This was again repeated at age 3 months or older. Older family members also had hemoglobin electrophoresis done to ascertain the patient's exact hemoglobinopathy. Between June 1974 and June 1986, SCD was diagnosed in 69 infants born at the University of Cincinnati Hospital. The charts of 68 of these patients were available for review. For each infant with SCD, two control infants were randomly computer selected by a biostatistician "blinded" to measures of jaundice in the infants after matching for the following factors known to affect neonatal jaundice14,15: gestational age by examination (±2 weeks), birth weight (±500 g), birth weight category (large, appropriate, and small for gestational age), race, and sex. Birth within the same year of the infants with SCD was attempted, except for three neonates with SCD born in 1986 who were matched with infants born in 1985, as computer records for 1986 were incomplete at the time of our chart review. The charts of these 68 patients with SCD and 136 controls were reviewed.

The information recorded for the study included the following: (1) drugs taken during pregnancy; maternal smoking, alcohol ingestion, and other substance abuse; (2) the presence or absence of maternal diabetes; (3) route of delivery and Apgar scores; (4) gestational age by dates and physical examination at birth, birth weight, birth weight category, sex, and race; (5) the presence and extent of any bruising, cephalhematomas, and intracranial bleeds; (6) vitamin K dose administered at birth; (7) the presence or absence of splenomegaly; (8) hemoglobin electrophoresis pattern at birth and at 3 months of age or later in patients with SCD; (9) blood group of infant/mother, Coombs' test results, red blood cell glucose-6-phosphate dehydrogenase screening (when done), and red blood cell structure; (10) evidence of intrauterine or neonatal infection; cordblood IgM concentrations, serum toxoplasmosis, rubella, cytomegalovirus, and herpes (TORCH) titers; blood, cerebrospinal fluid, and urine culture results when done; (11) all recorded blood hematocrits and age when done, to the nearest hour (hematocrit was recorded regardless of the site from which the blood was obtained and whether it was determined by way of centrifugation or by a counter [Coulter] in our clinical laboratory); (12) the use of phototherapy lights; (13) type of transfusions received; and (14) serum total and direct bilirubin concentration and age to the nearest hour when these were measured; the presence or absence of clinical jaundice. The duration of phototherapy, when performed, did not appear well documented; hence, we did not analyze this factor. Fluid intake, breast milk feeding, and mode of feeding may affect bilirubin concentrations in the neonate16 but were not controlled in our study, assuming that random selection of control would correct for this effect.

Infants with a serum bilirubin concentration equal to or greater than 85.5 µmol/L (5 mg/dL) were assumed to be clinically jaundiced even if this was not noted in the chart as such17 and were added to the group of clinically jaundiced infants for the purposes of analysis. All infants with SCD were black. In two instances control infants were of Asian (Indian) origin; in case of any

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possible bias, analysis with and without these infants was done; analyses gave the same results and hence the latter infants remained in the sample without replacement by substitute control infants.

Data were managed and analyzed using Statistical Analysis System (SAS Inc. Cary, NC). Analysis methods used were t test for the continuous variables to compare infants with SCD with control infants. and x2 or Fisher's exact test as appropriate for comparison using the categorical variables. Since it was impossible to pairmatch for every confounding variable that may affect bilirubin concentration, we elected to obtain two control patients for each patient with SCD and match for five major factors with this approach. Paired tests could not be used for analysis. Since multiple comparisons were performed between the SCD and the control group, every significant difference was restudied with a Bonferroni correction factor. 18

RESULTS

In addition to the matching variables, the patients with SCD and their controls proved well-matched for gestational age by history and were comparable for all maternal and obstetrical factors listed previously, including route of delivery (Table 1). There were no differences in types of drugs taken by the mothers during pregnancy. Maternal tobacco usage, alcohol ingestion, and substance abuse appeared poorly documented but were not different between groups.

The mothers of one control infant and two infants with SCD were White19 class A diabetic subjects while the mother of a third infant with SCD was a White class B diabetic subject. Data analysis with or without these infants gave the same results. All control patients had normal hemoglobin electrophoretic patterns. When infants with SCD and control infants were compared for the presence of clinically detectable jaundice and highest bilirubin concentration recorded within the first three days of life, there were no significant differences (Tables 2 and 3). The highest bilirubin concentration recorded (serum bilirubin $\geq 85.5 \, \mu \text{mol/L} \, [\geq 5 \, \text{mg/dL}])$ and clinical jaundice for patients with homozygous (SS) or S-hemoglobin C (SC) disease, and their controls, were similar (Table 3).

With the exception of a single con-

Table 1.—Comparison of Matching Criteria for Patients With Sickle Cell Disease (SCD) vs Controls*

| | Patients With SCD (N = 68) | Controls (N = 136) |
|---|----------------------------|-----------------------|
| Mean (±SD) gestational age by Dates, wk | 39.1 ± 2.5 (N=63) | 39.0 ± 2.7 (N = 127) |
| Examination, wk | 39.4 ± 2.0 | 39.4 ± 2.0 |
| Mean (±SD) birth weight, g | 3093 ± 571 | 3063 ± 538 |
| Sex F, No. (%) | 39 (57) | 78 (57) |
| M, No. (%) | 29 (43) | 58 (43) |
| Maternal diabetes, No. (%) | 3 (4) | 1 (1) |

^{*}P value was not significant in all instances.

Table 2.—Serum Bilirubin Concentration and Jaundice in Patients With Sickle Cell Disease (SCD) vs Controls

| | Patients With | Controls | |
|---|-----------------------------------|-------------------------------|----------|
| | SCD (N = 68) | (N = 136) | P Value* |
| Bilirubin measured, No. (%) | 28 (41) | 39 (29) | .052 |
| Highest (mean ± SD) serum bilirubin, μmol/L (mg/dL) | 145.35 ± 61.56 (8.5 ± 3.6) | 143.64 ± 73.53 (8.4 ± 4.3) | NS |
| Serum bilirubin, ≥85.5 μmol/L (≥5 mg/dL), | | | |
| No. (%) | 23/68 (34) | 32/136 (24) | NS |
| Clinical jaundice, No. (%) | 33/68 (48) | 69/136 (51) | NS |

^{*}NS indicates not significant.

Table 3.—Highest Serum Bilirubin Concentration and Jaundice in Patients With Homozygous (SS) Disease and S-Hemoglobin C (SC) Disease vs Controls

| | SS (N = 41) | Control (N = 82) | P Value* | SC (N = 17) | Control (N = 34) | P Value* |
|--|-------------------------------|-------------------------------|-------------|-------------------------------|-------------------------------|-------------|
| Bilirubin measured, No. (%) | 15 (36) | 16 (20) | .049 | 6 (35) | 17 (50) | NS |
| Highest bilirubin, µmol/L (mg/dL)† | 138.51 ± 47.88 (8.1 ± 2.8) | 150.48 ± 63.27 (8.8 ± 3.7) | NS | 141.93 ± 102.6 (8.3 ± 6.0) | 133.38 ± 92.34 (7.8 ± 5.4) | NS |
| Bilirubin ≥85.5 μmol/L (≥5 mg/dL), No. (%) | 12/41 (30) | 14/82 (17) | NS | 4/17 (24) | 12/34 (35) | NS |
| Clinical jaundice, No. (%) | 18/41 (44) | 36/82 (44) | NS | 8/17 (47) | 22/34 (65) | NS |

^{*}NS indicates not significant. †Values are mean ± SD.

trol patient, all patients had their blood hematocrit contents determined. The highest hematocrits for patients with SCD and control patients were similar (Table 4). Within the subgroups of patients with SS and SC disease and their controls, there were similarly no differences in their highest hematocrits (Table 5).

Six patients with SCD and eight control patients had ABO blood group incompatibility with their mothers, while three and four of either group, respectively, were Rh incompatible. One patient with SCD and four control patients had a positive direct Coombs' test. Only one control infant underwent an "exchange" blood transfusion. One patient with SCD and four control patients had a partial exchange transfusion for polycythemia, while one infant in each group received a packed

| 50P. | | | | | | | | | 100 | | | | | | | | | | | | | | | | | | | | | | |
|------|------|--------|-----|-------|--------|---------|-------|-------|-------|------|--------------|-----|------|------|------|-------|----------|-------|-------------|------|-------|-------|-------|-------|------|-------|-----|--------|--------|---------|-----|
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| a. | 788 | 60.0 | 200 | 30E | 0355 | diam | occió | 200 | 25 X | 630 | 678 3 | 227 | æν. | 30.0 | 48.4 | 20.00 | 0.0 | 22.5 | 1000 | 7.0 | an a | - 32 | 3 5 W | 10.15 | - 11 | 25 | 440 | 350.71 | 44 I T | 4.43 | |
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| | Patients With SCD (N = 68) | Controls (N = 136) | | | |
|---|------------------------------------|------------------------------------|--|--|--|
| Apgar score, min 1 | 7.2 ± 2.0 | 7.5±2.0 | | | |
| . 5 | 8.6 ± 1.1 | 8.7 ± 1.0 | | | |
| Serum IgM, g/L (mg/dL) | $0.107 \pm 0.041 \ (10.7 \pm 4.1)$ | $0.116 \pm 0.075 \ (11.6 \pm 7.5)$ | | | |
| Serum IgM ≥0.22 g/L (≥22 mg/dL), No. (%) | 1 (2) | 8 (7) | | | |
| Highest blood hematocrit, % | 60.4 ± 8.4 | 60.7 ± 7.5 | | | |
| Highest hematocrit in first 12 h, % | 57.3 ± 8.5 | $58.7 \pm 8.^{-}$ | | | |
| Contained hemorrhages, No. (%) | 12 (18) | 10 (7) | | | |

^{*}P value was not significant in all instances. Values are mean ± SD unless otherwise indicated.

Table 5.—Factors Predisposing to Jaundice in Patients With Homozygous (SS)
Disease and S-Hemoglobin C (SC) Disease vs Their Respective Controls*

| | SS | Control | sc | Control |
|---|-----------------------------------|------------------------------|-----------------------------------|------------------------------|
| | (N = 41) | (N = 82) | (N = 17) | (N = 34) |
| Apgar score, min | | | | |
| 1 | 7.2 ± 2.1 | 7.5 ± 2.0 | 7.0 ± 2.2 | 7.7 ± 1.8 |
| 5 | 8.7 ± 0.8 | 8.6 ± 0.9 | $\textbf{8.2} \pm \textbf{1.7}$ | 8.7 ± 1.1 |
| Highest hematocrit in first 12 h, % | 56.6 ± 8.3 | 57.8 ± 8.5 | 55.8 ± 8.2 | 59.6 ± 7.6 |
| Highest hematocrit, % | 59.2 ± 7.4 | 60.5 ± 7.4 | 60.1 ± 10.7 | 61.7 ± 7.9 |
| lgM, g/L (mg/dL) | 0.107 ± 0.039 (10.7 ± 3.9) | 0.116 ± 0.08 (11.6 ± 8.0) | 0.107 ± 0.045 (10.7 ± 4.5) | 0.118 ± 0.07 (11.8 ± 7.0) |
| Contained hemorrhages, No. (%) | 5 (12) | 4 (5) | 6 (35) | 4 (12) |

^{*}P value was not significant in all instances. Values are mean ± SD unless otherwise indicated.

red blood cell transfusion for anemia. Cord-blood IgM concentration was 0.22 g/L (22 mg/dL) or greater in one (1%) of 53 patients with SCD and eight (6%) of 117 controls (not significant). In none of these nine patients was a TORCH infection confirmed.

Forty-seven patients with SCD and 64 control patients had red blood cell film reports. None had sickled cells seen. Twelve (18%) patients with SCD and ten (7%) control patients had a contained hemorrhage (cephalhematoma, bruising); this is not significant after Bonferroni correction (Table 4). No patient had a head ultrasound examination. There were no differences between groups in the rate of culture-positive neonatal sepsis, vitamin K dose administered at birth, or presence of splenomegaly.

COMMENT

Our study did not demonstrate an association between SCD and neonatal

jaundice. All reports to date on this topic comprise either small groups of patients or isolated case reports and. with the exception of that of Wijgerden⁶ in 1983, were selected for patients with SCD who were clinically jaundiced or ill during the neonatal period. The largest study comprised 14 patients with SS disease whose conditions were diagnosed in a statewide, cord-blood screening program; nine infants (64%) had jaundice. 6 Combining all previously published reports, 17 (74%) of 23 patients with SCD detected in the neonatal period were jaundiced. These reports, however, had no control patients and did not examine factors that may affect neonatal jaundice.

To our knowledge, our study represents the largest such review (68 patients) done in patients diagnosed at birth as having SCD and is the only one in which well-matched control subjects were used. With an expected rate

of clinical jaundice in infants with SCD of 74% and an actual rate of 51% in our control infants, the power of our study to detect such a difference is 80%. ²⁰ The effect of birth weight, gestational age, race, and sex on the rate of neonatal jaundice is well known ^{14,15} and was controlled for in our study. Forty-eight percent (33/68), 44% (18/41), and 47% (8/17) of our patients with SCD, SS disease, and SC disease, respectively, and a similar percent of their respective controls were clinically jaundiced (Tables 2 and 3), which falls within the generally accepted range. ¹⁷

The main limitation of our study is its retrospective nature. However, the case-control design diminishes the effect of major confounding variables on our results and is likely to give results similar to those of a prospective study done along the same lines.21 Apart from highest bilirubin concentration, we also arbitrarily analyzed all patients with serum bilirubin concentrations of equal to or greater than $85.5 \mu mol/L$ (5 mg/dL) (Tables 2 and 3). Clinical jaundice generally can be detected in neonates with bilirubin concentrations of greater than 85.5 to 119.7 µmol/L (5 to 7 mg/dL), 17 but skin pigmentation may affect detection.14 All our study and control patients were of a dark complexion. A trend toward an increased rate of determination of serum bilirubin concentrations in patients with SCD vs controls (Tables 2 and 3) might reflect an increased rate of clinically perceived jaundice in infants with SCD or expectations that hyperbilirubinemia might be more frequent in such infants. Since documentation of phototherapy duration was inadequate, any effect it had in blunting peak serum bilirubin concentrations could not be accurately assessed.

Contrary to other reports, 3.5-7.8 there was no evidence of a higher rate of hemolytic jaundice secondary to either a major blood group incompatibility or sickled red blood cells of patients with SCD vs control patients. Contained hemorrhages may increase the rate of neonatal jaundice. 17 There was an increased rate of contained bleeds in patients with SCD vs their controls (Tables 4 and 5). Due to the number of analyses performed, this

could merely be an artifact of chance. With a Bonferroni correction¹⁸ factor for multiple analyses, this difference is not significant.

Blood hematocrit results in the neonate depend on time of sampling, site from which blood is obtained,²² and the method of determination.²³ Comparability among groups studied for this factor cannot be precisely verified. None of the infants was evaluated for glucose-6-phosphate dehydrogen-

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ase activity.

In summary, we found no increase in the rate of highest bilirubin concentrations or "clinical jaundice" in neonates with SCD vs normal controls within the first three days of life. We speculate that the reason for no difference in the rate of jaundice between the groups is the protective effect of a high intracellular hemoglobin F concentration in the neonate, preventing red blood cell sickling and hemolysis²⁴

and delaying the onset of clinical signs, typical of SCD, until after the third month of life.²⁵

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Reginald Tsang, MD, assisted with this study, the staff of the Hemoglobin Electrophoresis Laboratory provided all the information we requested, and Mary Brunner typed the manuscript.

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Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: Preliminary Results

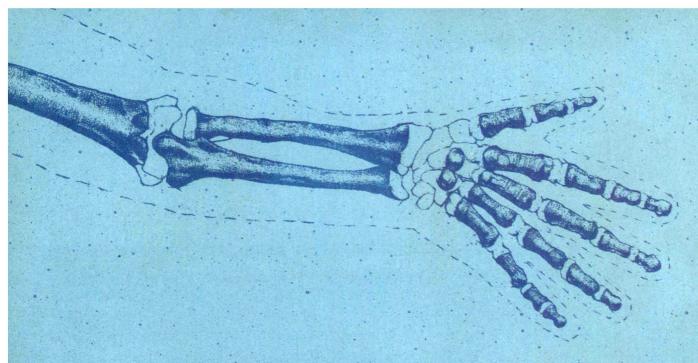
Cryotherapy for Retinopathy of Prematurity Cooperative Group

We report the preliminary three-month outcome of a multicenter randomized trial of cryotherapy for treatment of retinopathy of prematurity (ROP). Transscleral cryotherapy to the avascular retina was applied in one randomly selected eye when there was threshold disease (defined as five or more contiguous or eight cumulative 30° sectors [clock hours] of stage 3 ROP in zone 1 or 2 in the presence of "plus" disease). An unfavorable outcome was defined as posterior retinal detachment, retinal fold involving the macula, or retrolental tissue. At this writing, 172 infants had been examined three months after randomization. An unfavorable outcome was significantly less frequent in the eyes undergoing cryotherapy (21.8%) compared with the untreated eyes (43%). While the surgery was stressful, no unexpected complications occurred during or following treatment. These data support the efficacy of cryotherapy in reducing by approximately one half the risk of unfavorable retinal outcome from threshold ROP. (Arch Ophthalmol 1988;106:471-479).

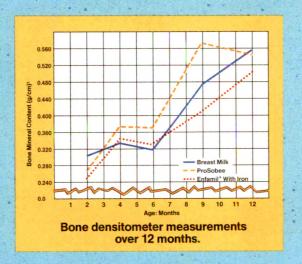


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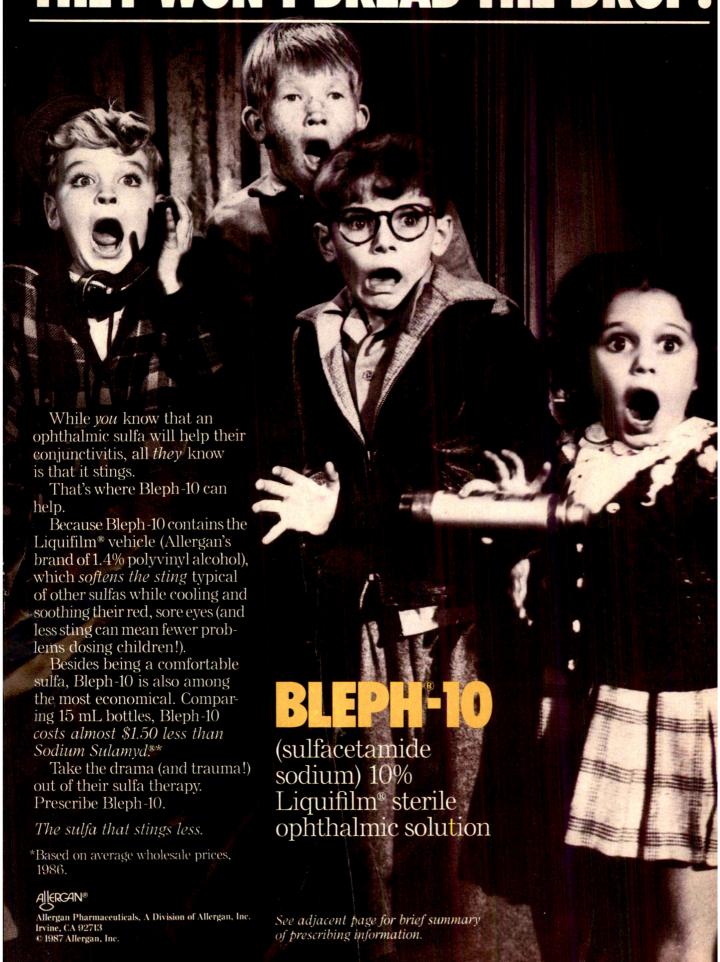
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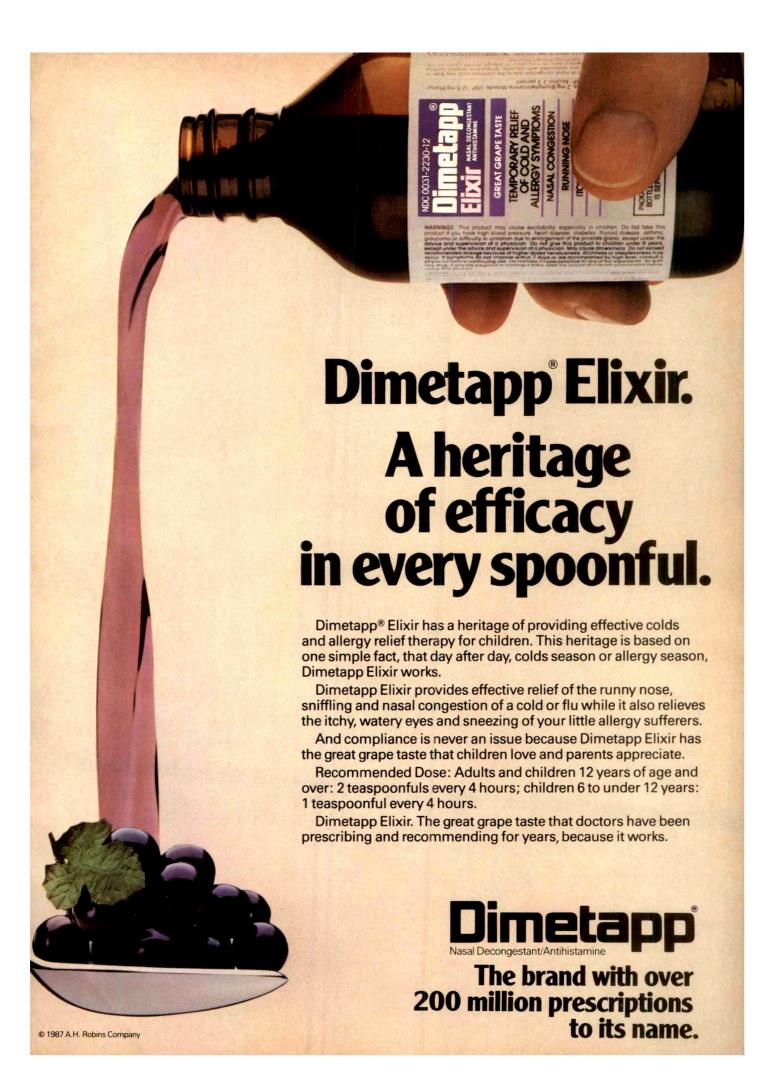
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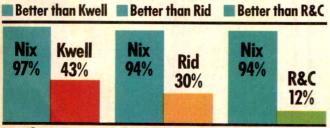
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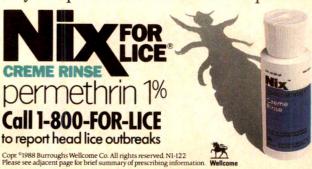
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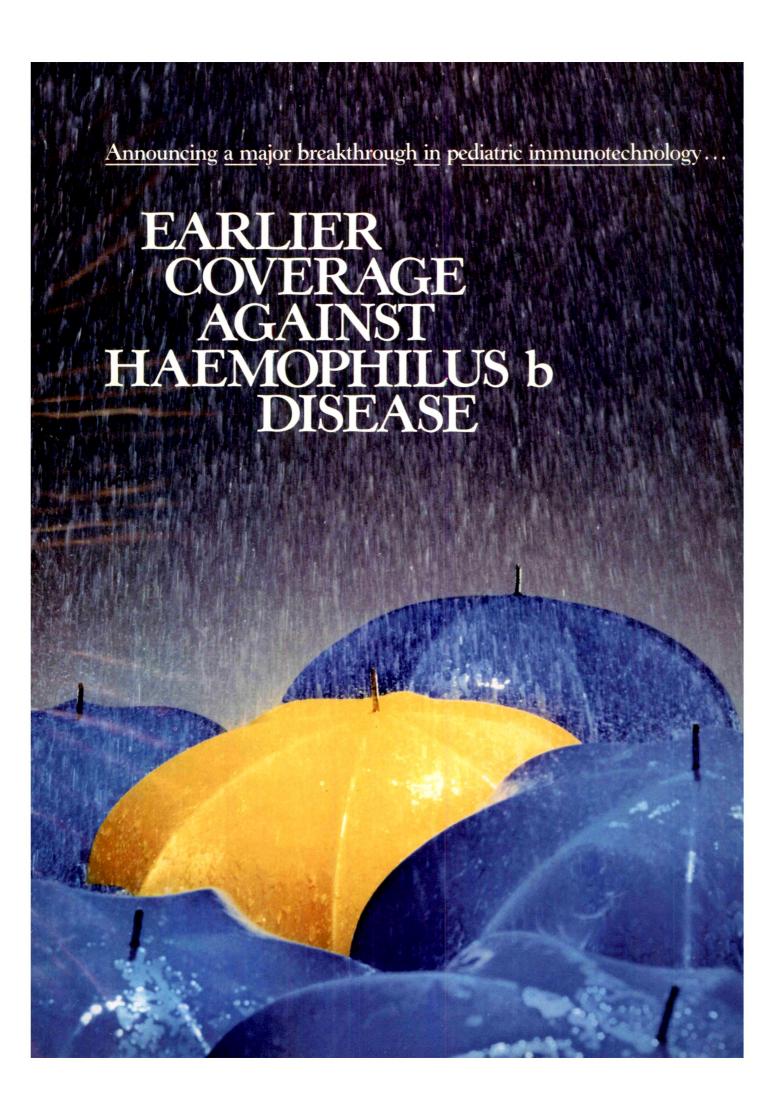
The Department of Pediatrics at Emanuel Hospital & Health Center is seeking a full-time Chief of Pediatrics responsible for the leadership of a busy regional pediatric center consisting of a 45 bed NICU, 48 bed pediatric unit, 6 bed ICU, an active ambulatory department and an extensive spectrum of pediatric medical and surgical services.

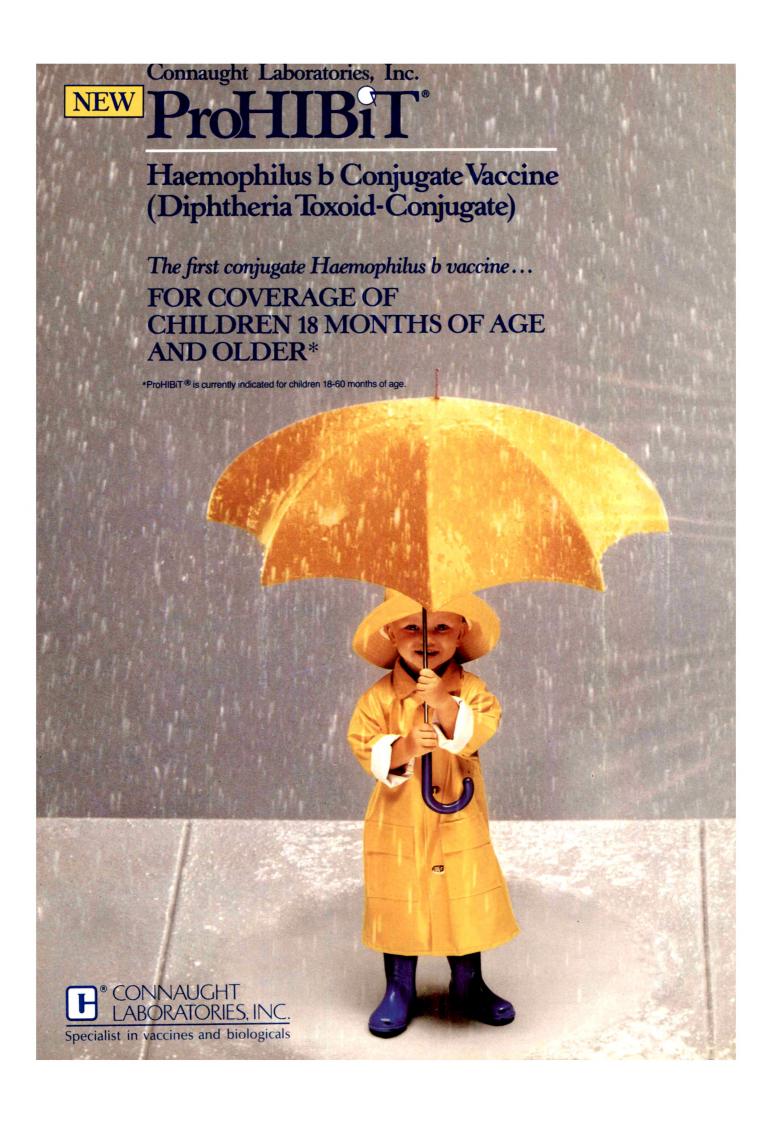
The program has strong community pediatrics roots but includes a wide range of tertiary care services including ECMO, regional burn unit, regional child abuse program, EEG telemetry, pediatric and neonatal transport and open heart surgery.

A physician possessing administrative skills and academic orientation with experience in a subspecialty or general pediatrics practice is desired.

Interested candidates, please contact:

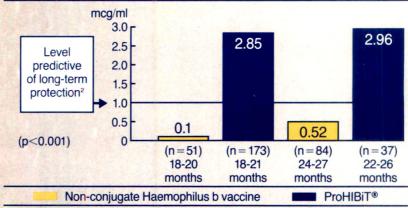
Delores Orfanakis, M.D. Emanuel Hospital & Health Center 2801 N. Gantenbein Avenue Portland, Oregon 97227 (503) 280-4637





Proven immunogenicity against Haemophilus b disease in children 18-23 months of age ProHIBiT® consistently produces antibody levels (GMT)[†] predictive of long-term protection (≥1.0 mcg/ml) in children 18-23 months of age[‡] — unlike non-conjugate Haemophilus b vaccines.^{1,2}

Antibody levels produced by ProHIBiT® 29-fold higher than those induced by non-conjugate Haemophilus b vaccines in children 18-20 months old¹

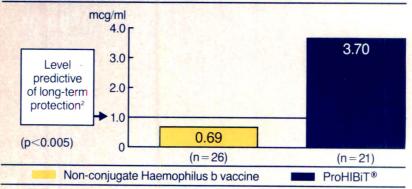


Multicenter study demonstrating mean rise in antibody titers in children 18-21 months and 22-26 months of age vaccinated with ProHIBiT® or non-conjugate Haemophilus b vaccine, as measured by RIA assay

‡A one-month post-immunization antibody level of ≥ 1.0 mcg/ml has been correlated with long-term protection against Haemophilus b disease.²

Superior antibody responses in children 24-60 months of age

ProHIBiT® consistently produced higher antibody levels (≥ 1.0 mcg/ml) than did non-conjugate Haemophilus b vaccine in children 23-24 months old¹



Multicenter study comparing antibody levels produced by ProHIBiT® and non-conjugate Haemophilus b vaccine in children 23-24 months of age

Haemophilus b Conjugate Vaccine is recommended by the AAP and ACIP*

*The American Academy of Pediatrics: *PedComm: AAP Member Alert*, February 3, 1988 and the Immunization Practices Advisory Committee: *MMWR*, January 22, 1988.

NEW

ProHIBiT° THE ONLY HAEMOPHILUS & VACCINE YOU NEED FOR CHILDREN 18-60 MONTHS OF AGE

Please see brief summary of prescribing information on last page of this advertisement.

[†]Geometric mean titer



NEW ProHIBiT[®]

Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate)

Safe, long-lasting coverage for children 18-60 months of age

No significant adverse reactions have been reported with ProHIBiT® after more than 120,000 vaccinations in 40,000 children. In fact, the rate and severity of adverse reactions observed with ProHIBiT® are not significantly different from placebo.1

The conjugated Haemophilus b polysaccharide antigen in ProHIBiT® enhances the antibody response of the child's immune system. 90% of children vaccinated with ProHIBiT® continued to demonstrate protective antibody levels when titers were measured one year after vaccination.1 And unlike non-conjugate Haemophilus b vaccines, no booster is needed with ProHIBiT®1

Easy to administer

Immunization with ProHIBiT® can be scheduled with a child's other routine vaccinations. ProHIBiT® is supplied in convenient 1-dose, 5-dose and 10-dose vials, and requires no reconstitution.

To order, please call toll-free 1-800-VACCINE (1-800-822-2463). For technical information, call the toll-free ProHIBiT® Hot Line at 1-800-533-5441.

Please see brief summary of prescribing information on following page of this advertisement.

NEW ProHIBiT®

THE ONLY HAEMOPHILUS & VACCINE YOU NEED FOR CHILDREN 18-60 MONTHS OF AGE



ProHIBi

Haemophilus b Conjugate Vaccine (Diphtheria Toxoid-Conjugate)

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

BRIEF SUMMARY

INDICATIONS AND USAGE

ProHIBIT is indicated for the routine immunization of children 18 months to 5 years of age against invasive diseases caused by Haemophilus influenzae type b As with other vaccines, several days following administration of ProHIBiT are required for protective levels of antibody to be attained.

A booster dose of ProHIBiT is not required

ProHIBIT will not protect against Haemophilus influenzae other than type b or other microorganisms that cause meningitis or septic disease.

No impairment of the immune response to the individual antigens was demonstrated when ProHIBIT and Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP) were given at the same time at separate sites

Because the safety and efficacy of ProHIBIT have not been established in children less than 18 months of age, ProHIBIT is not indicated for use in this age group at this time. Studies to establish the safety and efficacy of ProHIBiT in children less than 18 months of age are ongoing

ProHIBIT IS NOT RECOMMENDED FOR USE IN CHILDREN YOUNGER THAN 18 MONTHS OF AGE.

CONTRAINDICATIONS

HYPERSENSITIVITY TO ANY COMPONENT OF THE VACCINE, INCLUDING THI-MEROSAL AND DIPHTHERIA TOXOID, IS A CONTRAINDICATION TO USE OF THIS VACCINE.

WARNINGS

If ProHIBIT is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

As with any vaccine, ProHIBiT may not protect 100% of individuals receiving the vaccine

PRECAUTIONS

GENERAL

As with the injection of any biological material, Epinephrine Injection (1:1000) should be available for immediate use should an anaphylactic or other allergic

Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse reactions. This includes a review of the patient's history with respect to possible hypersensitivity to the vaccine or similar vaccines

Any febrile illness or acute infection is reason to delay the use of ProHIBiT. As reported with Haemophilus b polysaccharide vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccine

Special care should be taken to ensure that the injection does not enter a blood vessel

A separate, sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ALTHOUGH SOME IMMUNE RESPONSE TO THE DIPHTHERIA TOXOID COMPO-NENT MAY OCCUR, IMMUNIZATION WITH ProHIBIT DOES NOT SUBSTITUTE FOR ROUTINE DIPHTHERIA IMMUNIZATION.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY ProHIBiT has not been evaluated for its carcinogenic, mutagenic potential or impairment of fertility.

REPRODUCTIVE STUDIES — PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with ProHIBiT. It is also not known whether ProHIBiT can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ProHIBIT is NOT recommended for use in a pregnant woman.



ADVERSE REACTIONS

When ProHIBIT alone was given to over 1,000 adults and children, no serious adverse reactions were observed. Thrombocytopenia was seen in one adult but a causative relationship was not established.

When ProHIBiT was given with DTP and Inactivated Poliovirus Vaccine to 30,000 young infants, the rate and extent of serious adverse reactions were not different from those seen when DTP was administered alone. Allergic reactions such as urticaria were infrequently observed.

Selected adverse reactions following vaccination with ProHIBiT (without DTP) in subjects 16-24 months of age are summarized in Table.

Percentage of Subjects 16-24 Months of Age Developing Local Reactions or Fever to One Dose of Haemophilus b Conjugate Vaccine (Diphtheria Toxold-Conjugate)

| | at mark Principles and commend a limited delines property of the commend of the commend as a black | | Reaction % | |
|---------------|--|--|------------|----------|
| | No. of Subjects* | 6 Hours | 24 Hours | 48 Hours |
| Fever >38.3°C | 281 | 1.1 | 2.1 | 1.8 |
| Erythema | 285 | AUGUSTUS. | . 2.5 | 0.4 |
| Induration | 285 | weaken two | 1.0 | 0.4 |
| Tenderness | 285 | The Contraction of the Contracti | 4.6 | 0.7 |

Not all subjects had measurements at all time periods

Other adverse reactions temporally associated with administration of ProHIBiT included diarrhea, vomiting, and crying and occurred at a frequency of \$1.2%.

Adverse reactions in clinical evaluations among 689 children, 7-14 months of age, 24 hours after receiving a single dose of ProHIBIT, were observed and compared to 139 children who received a saline placebo. There were no significant differences in the reaction rates for fever, erythema, induration, and tenderness between the two groups

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, vaccine should not be administered

ProHIBiT is indicated for children 18 months to 5 years of age. The immunizing dose is a single injection of 0.5 ml given intramuscularly in the outer aspect area of the vastus lateralis (mid-thigh) or deltoid.

Each 0.5 ml dose contains 25 mcg of purified capsular polysaccharide and

18 mcg of conjugated diphtheria toxoid protein.

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel

DO NOT INJECT INTRAVENOUSLY.

HOW SUPPLIED

Vial, 1 Dose (5 per package) - Product No. 49281-541-01

Vial, 5 Dose — Product No. 49281-541-05

Vial, 10 Dose - Product No. 49281-541-10

STORAGE

Store between 2°-8°C (35°-46°F). DO NOT FREEZE

REFERENCES: 1. Data on file, Connaught Laboratories, Inc. 2. Peltola H. et al. Prevention of *Haemophilus influenzae* type b infections with the capsular polysaccharide vaccine. *N Engl J Med* 1984;310:1561-1566.



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Instructions for Authors

NEW MANUSCRIPT PROCEDURE

On Jan 1, 1988, AJDC initiated a new procedure. Manuscripts submitted to AJDC will NO LONGER BE RETURNED, except in the case of accepted manuscripts or those undergoing author revision. Original artwork and photographs will be returned.

General Information.—Please send manuscripts and correspondence by first-class mail (do not use registered, certified, or express mail) to the Editor, Vincent A. Fulginiti, MD, AJDC, PO Box 43700, Tucson, AZ 85733. All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Reprints are shipped six to eight weeks after publication. Proofs will be sent for approval if requested by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Conforming with all of the steps listed below will facilitate the editorial processing of your manuscript.

Step 1.—Cover Letter. — All manuscripts must be accompanied on submission by a cover letter giving the name, address, affiliation, and telephone number of the corresponding author. The letter must include ALL of the following statements SIGNED BY ALL AUTHORS (ORIGINAL SIG-NATURES):

- 1. Copyright Release. "In consideration of the American Medical Association's taking action in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership to the AMA in the event that this work is published by the AMA."
- 2. Statement of Affirmation. "This manuscript has not been published anywhere in any language and is not under simultaneous consideration by another publication. This manuscript is original and ALL authors have seen and approve of its contents."
- 3. Financial Disclosure.-List all affiliations with or financial involvement in organizations or entities with a direct financial interest in the subject matter or material of the research discussed in the manuscript (eg. employment consultancies, stock ownership) OR include a statement disclaiming any such involvement. All such information will be held in confidence during the review process. Should the manuscript be accepted, the Editor will discuss with the author the extent of disclosures appropriate for publication. All accepted manuscripts become the permanent property of the publisher (AMA) and may not be published elsewhere without written permission from the AMA. After publication certain articles may appear in translation in the foreign-language edition(s) of AJDC.
- Step 2.-Manuscript Format.-All articles submitted should have the following features:
- 1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.
- 2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm ($81/2 \times 11$ in) with 2.5-cm (1-in) margins. Do not use justified right margins.
- 3. Title should be no more than 75 characters.
- 4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.
- 5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.
- 6. Writing style should conform to proper English usage and syntax; consult AMA's Manual for Authors & Editors, available from Prentice Hall Inc. 200 Old Tappan Rd, Old Tappan, NJ 07675.
 - 7 Abstract should be limited to 135 words or less.
- 8. Each table should be typed, with a title, on a separate sheet of paper, with each line, including headings, double-spaced. Continuations should be on a second sheet with all headings repeated.
- 9. Use Système International (SI) measurements throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text in accordance with AMA policy.
- 10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed label and affixed on the back of each illustration. Do not write directly on the print.

Magnification and stain should be provided for histologic sections. Full-

color illustrations should be submitted as 35-mm, positive color transparencies, mounted in cardboard and carefully packaged. Do not submit glass-mounted transparencies or color prints. Fee is \$400 for up to six square-finished color illustrations that fit on one page. A letter of intent to pay the fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from both parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, typed double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below.

Journal Articles: Sell EJ, Gaines JA, Gluckman C, et al: Persistent fetal circulation: Neurodevelopmental outcome. AJDC 1985;139:25-28.

Books: Krmpotic-Nemanic J, Kostovis I, Rudan P: Aging changes of the form and infrastructure of the external nose and its importance in rhinoplasty, in Conly J, Dickinson JT (eds): Plastic and Reconstructive Surgery of the Face and Neck. New York, Grune & Stratton, 1972, pp 84-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

- 12. Investigations involving human subjects require a specific statement in the "Methods" section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.
- 13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from publisher and author. Brief acknowledgments to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgments will be deleted.

Step 3.-Special Departments.-Criteria for several special departments are given below.

- 1. The Pediatric Forum. This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of AJDC. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED "FOR PUBLICATION" AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.
- 2. From Research to Relevance.—PURPOSE: To focus on significant research that has a high probability of being translated into elinical usefulness.
- 3. Educational Interventions. PURPOSE: To share information concerning any educational efforts in the broad field of pediatrics.
- 4. Sports Medicine.—Purpose: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.
- 5. Picture of the Month. Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.
- 6. Radiological Case of the Month. Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

| Author's | Check | list |
|----------|-------|------|
| | | |

| | | Author's Checklist |
|---|-----|---|
| | 1. | Cover letter with name, address, and telephone number of corresponding author. |
| | 2. | Copyright transmittal, affirmation, and financial statements signed by ALL authors. |
| | 3. | Original typed manuscript plus three copies. |
| | 4. | Triple-spacing; double-spacing for tables and legends. |
| | 5. | Right margins UNJUSTIFIED. |
| | 6. | Title 75 characters or less. |
| | 7. | Abstract included. |
| *************************************** | 8. | References in proper format, cited in numerical order. |
| | 9. | Four sets of illustrations. |
| | 10. | Four sets of legends for illustrations. |
| | | Proper consent forms for patient photographs. |
| | | Permission forms for illustrations previously published elsewhere |



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References: 1. Oberfield SE, Levine LS: The child with short stature: NY State J Med; Essays in pediatrics; Jan 1986, 15-21.

2. Growth hormone in the treatment of children with short stature. Report of Ad Hoc Committee on Growth Hormone Usage, the Lawson Wilkins Pediatric Endocrine Society and Committee on Drugs AAP Pediatrics 1983; 72:891-94. 3. (Glasbrenner K: Technology spurt resolves growth hormone problem, ends shortage; JAMA, 1986, 255 (5) 581-587. 4 Rosentled RG, Hintz RL: Diagnosis and management of growth disorders; Drug Therapy, May 1983, 61-76. 5. Growth and growth hormone: Disorders of the anterior pituliary, in Kaplan SA: Clinical Pediatric and Adolescent Endocrinology, WB Saunders Co. 1982. 6. Underwood LE, Rosentled RG, Hintz RL: Human Growth and Growth Disorders: An Update, University of North Carolina School of Medicine and Stanford University School of Medicine, October 1985.

Brief summary of prescribing information

PROTROPIN* (somatrem for injection)
INDICATIONS AND USAGE Protropin (somatrem for injection) is
indicated only for the long term treatment of children who have
growth failure due to a lack of adequate endogenous growth hormone secretion. Other etiologies of short stature should be

mone secretion. Other etiologies of short stature should be excluded.

CONTRAINDICATIONS Protropin (somatrem for injection) should not be used in subjects with closed epiphyses. Protropin growth hormone should not be used when there is evidence of any progression of underlying intracranial lesion. Intracranial lesion must be in-active and antitumor therapy complete prior to instituting therapy. Protropin growth hormone should be discontinued if there is evidence of recurrent tumor growth. Protropin growth hormone, when reconstituted with Bacteriostatic Water for injection, USP (Benzyl Alcohol Preserved) should not be used in patients with a known sensitivity to benzyl alcohol.

WARNINGS Benzyl alcohol as a preservative in Bacteriostatic Water for Injection, USP USE ONLY ONE DOSE PER VIAL AND DISCARD THE INNUSED PORTION.

for Injection, USP USE ONLY ONE DOSE PER VIAL AND DISCARD THE UNUSED PORTION.

PRECAUTIONS Portropin (somatrem for injection) should be used only by physicians experienced in the diagnosis and management of patients with pituitary growth hormone deficiency. Patients with growth hormone deficiency secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process. Because Protropin growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance. Concomitant glucocorticoid therapy may inhibit the growth promoting effect of Protropin growth hormone. Patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth. Hypothyroidism may develop during Protropin treatment. Untreated hypothyroidism prevents optimal response to Protropin growth hormone. Therefore, patients should have periodic thyroid function tests and should be it reated with thyroid hormone when indicated. See WARNINGS for use of Bactenostatic Water for Injection, USP (Benzyl Alcohol Preserved) in new Years and Patrons.

ADVERSE REACTIONS

Bacteriostatic Water for Injection, USP (Benzyl Alcohol Preserved) in newborns:

ADVERSE REACTIONS
A. Protropin (somatrem for injection) Approximately 30 percent of all Protropin formatrem for injection) Approximately 30 percent of all Protropin treated patients developed persistent antibodies to growth hormone. In patients who had been previously treated with pituitary-derived growth hormone, one of twenty-two subjects developed persistent antibodies to growth hormone in response to Protropin therapy. In children not previously treated with any exogenous growth hormone approximately 40 percent developed persistent antibodies to growth hormone. In general, the growth hormone antibodies are not neutralizing and do not interfere with the growth response to Protropin growth hormone. One of eighty-four subjects treated with Protropin growth hormone. One of eighty-four subjects treated with Protropin growth hormone. One of eighty-four subjects treated with Protropin growth hormone for 6 to 36 months developed antibodies associated with high binding capacities and failed to respond to treatment with Protropin growth hormone should be carried out in any patient who fails to respond to therapy. Additional short term immunologic and renal function studies were carried out in a group of patients after approximately two years of treatment to detect other potential adverse effects of antibodies to growth hormone. The antibody was determined to be of the IgG class, no antibodies to growth hormone of the IgG class were detected. Testing included immune complex determination, measurement of total hemolytic complement and specific complement components, and immunochemical analyses. No adverse effects of growth hormone arithody formation were observed. These findings are supported by a toxicity study conducted in a primate model in which a similar antibodie and the same doses and with placebover a period of 90 days. Most monkeys treated with high-dose Pric tropin growth hormone developed persistent antibodies and persistent ant

was also examined for the presence of immune complexes and possible toxic effects of immune complexes by immunohistochemistry and electron microscopy.

Besterfects of immune complexes by immunohistochemistry and electron microscopy.

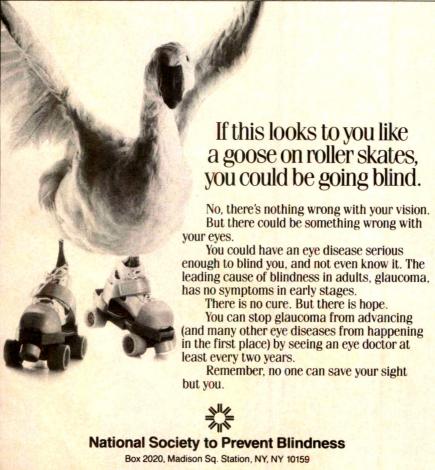
Besterfects the Water for Injection, USP (Benzyl Alcohol Preserved) Toxicily in newborns has been associated with benzyl alcohol as a preservative (see WARNINGS).

OVERDOSAGE The recommended dosage of up to 0.1 mg (0.2 IU) per kg body weight alcohol as a preservative for side effects.

DOSAGE AND ADMINISTRATION The Protropin (somatrem for injection) dosage must be individualized for each patient. A dosage and schedule of up to 0.1 mg/kg (0.2 IU/kg) body weight administered three times per week (i.i.w), by intramuscular injection is recommended. After the dose has been determined, reconstitute each 5 mg vial with 1.5 mL of Bacteriostatic Water for injection, USP (Benzyl Alcohol Preserved) in the vial seproximately 28. To prepare the Protropin atter reconstitution is seproximately 28. To prepare the Protropin solution, inject the Bacteriostatic Water for injection, USP (Benzyl Alcohol Preserved) into the vial of Protropin growth hormone, aiming the stream of liquid against the glass wall. Then swirt the product vial with a GENTLE rotary motion until the contents are completely dissolved. Do NOT SHAKE. It is recommended that Protropin growth hormone be administered using sterile, disposable syringes and needles. After reconstitution, vial contents should be clear, without particulate matter It is folution is cloudy or contains particulate matter the contents MUST NOT be injected. Before and after injections the septum of the vial with a sent and and an antiseptic solution to prevent contamination of the contents after repeated needle insertions. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy. The needle should to of small enough volume that the prescribed dose can be drawn from the muscular layer.

Genentech, Inc.

460 Point San Bruno Blvd. South San Francisco, CA 94080





Releasing the human potential for growth

PROTROPIN® (somatrem for injection): For children who need growth hormone

In the past, the limited supply of pituitary-derived growth hormone meant that only the most profoundly growth hormone-deficient children were treated.^{1,2}

Today, the recombinant DNA technology of Genentech ensures a virtually limitless supply of pure Protropin growth hormone for the treatment of all children lacking adequate endogenous growth hormone. Clinical studies of Protropin growth hormone, the most complete studies conducted for any growth hormone product, confirm its safety and efficacy in the treatment of this disorder.³

Some important clinical guidelines for patient identification

- Record height at all routine pediatric examinations.⁴
- Compare with cross-sectional data on a standard growth chart.⁴
- Careful, consistent technique for measuring children's height is critical.⁴
- Growth rates of less than 5 centimeters (2 inches) per year before age five, or less than 4.5 centimeters (1.8 inches) per year after age five, are cause for concern and may warrant further evaluation.⁵
- Progressive deviation from a normal growth curve may become apparent at any time during childhood.⁵
- Measurements made over four to six months, that show a decline in growth rate, may signal the need to refer the child for further evaluation.⁶

Early intervention: Time to grow

 Early diagnosis of children lacking adequate endogenous growth hormone is desirable because younger children typically demonstrate better responses to treatment and better long-term results than older children.⁶

For further information, please call toll free 1-800-821-8590 or 1-800-551-2231



X-ray child aged 8

Protropin [somatrem for injection]

A Pure Product of Biotechnology

Genentech, Inc.

Please see Protropin* (somatrem for injection) brief summary on adjacent page.

The Pediatric Forum

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

False Crystalluria With Super-Absorbent Disposable Diapers

Sin—In the interest of concerned parents, we would like to report an incident that may occur in infants wearing "super-absorbent" disposable diapers. Improvements in materials used for disposable diapers have minimized the usual problem of rash associated with wet diapers. This advancement has occurred through the use of improved components of the diaper, primarily greater absorbent gelling material that makes the diaper more effective in absorbing urine.

Occasionally, small, loose quantities of this material may pass through the top sheet of the diaper (especially if ruptured) and transfer to the infant's skin. This gel on the skin gives the appearance of small, shiny beads or a lotionlike film on the skin, or "crystals" being present in the infant's urine. Bagged or catheterized urine samples do not show the material in the urine. The new gelling material is being used more frequently in disposable diapers and has been thoroughly safety tested and is nontoxic.

The physician should be aware of the possible occurrence of gel on the skin or "false crystalluria" in infants wearing super-absorbent disposable diapers.

Frank W. McKemie, MD
Frank W. McKemie, MD
Paul T. McEnery, MD
Division of Nephrology
Children's Hospital Medical Center
University of Cincinnati
College of Medicine
240 Bethesda Ave
Cincinnati, OH 45229

Reprints can be obtained by writing to Dr McEnery.

Minimal Expression of the Beckwith-Wiedemann Syndrome and Bilateral Wilms' Tumor

Sir.—A 28-year-old gravida II, para I woman was referred for genetic counseling because of a Wilms' tumor in her previous child. Her daughter had been born at term, weighed 4.2 kg, and had a purplish birthmark over her forehead. Her neonatal course was uncomplicated. At age 1 year, her left leg and foot were found to be smaller than the right. At age 5 years, the finding of a large abdominal mass during a routine examination led to the diagnosis of bilateral Wilms' tumor. At age 9 years, the girl weighed 65 kg, was 139 cm tall, and had a faint fan-shaped midline nevus flammeus on her forehead. She had mild macroglossia but no dental malocclusion, earlobe creases, umbilical hernia, or diastasis recti. Her left foot was 1.5 cm shorter than the right. Her mother was 174 cm tall, weighed 122 kg, and had diastema between her upper central incisors. The mother's sister was said to walk with a limp because of a congenital leg-length discrepancy.

Prenatal and postnatal macrosomia, macroglossia, and midline nevus flammeus in this child suggested a diagnosis of Beckwith-Wiedemann syndrome (BWS), even though some of the more characteristic features of BWS were not present. It is known that BWS may be quite variable in expression and that no strictly defined minimal diagnostic criteria identify all patients with BWS. 1,2 Also, some of the features become less noticeable with age, and the conditions mildly affected relatives of patients with BWS may go undiagnosed.3 In this child, large size and midline nevus flammeus over the forehead were the

only signs present at birth, body asymmetry and accelerated growth being of later onset. She thus exemplifies the subtle ways in which BWS can present. Careful follow-up of such minimally affected infants with BWS is important because they also face a high risk of Wilms' tumor.⁴

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1. Cohen MM Jr, Ulstrom RA: Beckwith-Wiedemann syndrome, in Bergsma D (ed): Birth Defects Compendium of The National Foundation—March of Dimes. New York, Alan R Liss Inc, 1979, pp 140-141.

 Pettenati MJ, Haines JL, Higgins RR, et al: Wiedemann-Beckwith syndrome: Presentation of clinical and cytogenetic data on 22 new cases and review of the literature. Hum Genet 1986;74:143-154.

3. Niikawa N, Ishikiriyama S, Takahashi S, et al: The Wiedemann-Beckwith syndrome: Pedigree studies on five families with evidence for autosomal dominant inheritance with variable expressivity. Am J Med Genet 1986;24:41-55.

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Avoiding Anxiety About 'Innocent' Heart Murmur

Sin.—The following dialogue occurred in a pediatrician's office:

Pediatrician (after physical examination of child): "I heard a little heart murmur that I am pretty sure is innocent, but just to be sure I am going to make an appointment for Johnny to be seen by a pediatric cardiologist."

Mother: "Is it something to worry about?"

Pediatrician: "No, there is probably nothing wrong, but just to be on the safe side . . . "

Mother (thinking to herself): "He must have heard something bad if he is sending Johnny to a heart specialist. I wonder what could be wrong with his heart?"

Dr McNamara's editorial in the November issue of AJDC raised for me the question of how much needless parental worry, and even significant harm to children because of parental overprotectiveness, results when the specter of heart disease arises from these innocent referrals by primary care pediatricians. The term heart murmur, whether preceded by the adjective "innocent" or not, may lead to significant anxiety about, and/or restriction of physical activity by, a normal child, particularly if the parents have had personal experience with a friend or relative who had heart disease.2 Such a child is a prime candidate for developing "the vulnerable child syndrome."

To help prevent such unfortunate side effects of the diagnosis, innocent heart murmur, pediatricians may seriously consider spending the 15 minutes Dr McNamara suggests are needed to perform an adequate examination for innocent murmurs, at least once during a child's life. Pediatricians may thereby avoid sending a healthy child to a cardiologist, whose very title suggests that something is amiss with that most vital of body organs. The extra 15 minutes could save a lifetime of needless heartache.

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- 1. McNamara DG: The pediatrician and the innocent heart murmur. AJDC 1987:141:1161.
- innocent heart murmur. AJDC 1987;141:1161.

 2. Bergman AB, Stamm SJ: The morbidity of cardiac non-disease in school children. N Engl J Med 1967;276:1008-1013.
- 3. Green M, Solnit AJ: Reactions to the threatened loss of child: Vulnerable child syndrome: III. Pediatric management of the dying child. Pediatrics 1964;34:58-66.

In Reply.—The dialogue in Dr Hersher's letter will doubtless remind many pediatricians of problems that they have had with innocent heart murmurs, especially when trying briefly to explain one to the understandably distraught parent or anxious teenager.

To minimize referral of children with innocent murmurs to cardiac centers, Dr Hersher urges pediatricians to take the extra time required to perform a thorough cardiovascular, especially auscultatory, examination.

It is asking a lot, Dr Hersher, to expect the busy pediatrician to perform a complete and thorough cardiovascular examination on every patient with a presumably innocent murmur. It not only takes time but also requires virtually daily practice to perform the examination expertly. Once physicians start looking for innocent murmurs, one or more such murmurs can be heard in practically all children, and certainly in half of them. The fact is that most pediatricians accurately spot the common innocent murmurs (Still's murmur, pulmonary "flow" murmur, venous hum, and neonatal peripheral pulmonary artery murmur). But many pediatricians tell me that even when they feel certain a murmur is innocent, parents often insist on a consultation with a pediatric cardiologist.

I think one problem is that physicians often unwittingly project uncertainty to the parent by using a phrase such as that in Dr Hersher's letter, "there is probably nothing wrong," or "just to be on the safe side," or a physician may propose checking the murmur again on the next office visit.

Another aspect that creates anxiety for parents concerns their questions about heart murmurs in general that may not occur to them until after they have left the physician's office. A written explanation of innocent murmurs helps when time and the pressure of other patients waiting prevents the physicians from giving a clear explanation on the spot.

In my editorial, I offered to mail readers a copy of the article that I use to explain innocent murmurs to parents. Some 300 physicians around the country and abroad have asked for a copy. In addition to the ten or 15 minutes required for a thorough auscultatory examination, one can easily spend another ten to 15 minutes explaining innocent murmurs.

I would recommend to pediatricians who feel reasonably certain that a murmur is innocent based on their usual cardiac examination, no matter how brief of superficial, that they either say nothing at all, or if they feel that they should inform the family, simply state, "The heart sound that I hear is innocent and is a very common occurrence in well over half of all the healthy children that I see. In my opinion, no further test is necessary." Then give the parents a written explanation of innocent heart murmurs.

The third alternative is referral of troublesome cases to a pediatric car-

diologist. The disadvantage of doing that for only an innocent murmur is simply the expense in time and money. Dr Hesher is correct that neither restriction of physical activity nor other special precautions are warranted for a murmur detected after only a brief auscultation of the heart.

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Removal of Cactus Spines From the Skin

Sir—I read with interest the article about removal of cactus spines from the skin by Martinez et al¹ in the December 1987 issue of AJDC. The authors found the combination of tweezers and glue to be the most effective method of removing bunches of spines. However, the use of tweezers can be difficult in the young, uncooperative child, and glue application and drying can be time-consuming. The following report illustrates an alternative method of cactus spine removal in children.

Patient Report.—A 2-year-old girl presented to our emergency department after falling on a cactus plant display. She had multiple implantation of spines on her left hand and the lower third of her left forearm. She was agitated, crying, and unconsolable by her parents. Initial attempts to remove the spines using tweezers proved unsuccessful even after restraining the child. The attempt was aborted after a few minutes, and the child was given intramuscular midazolam for sedation. Hair removal wax (Hair-Off, Allegheny Corp) was applied to the affected areas and all spineseven the ones between her fingers-were removed in ten minutes. There was no skin reaction. Follow-up telephone contact after three weeks revealed no adverse reactions or complications.

Comment.—In conclusion, the use of Hair-Off wax appears to be an effective, rapid, and safe method for removal of cactus spines from the skin of young children.

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1. Martinez TT, Jerome M, Barry RC, et al: Removal of cactus spines from the skin: Comparative evaluation of several methods. *AJDC* 1987; 141:1291-1292.

Are Dinamap Blood **Pressures in Premature** Infants Reliable?

Sir.-A recent article in the October 1987 issue of AJDC by Wareham et al' demonstrated wide 95% prediction intervals (17 to 21 mm Hg) for systolic, diastolic, and mean blood pressures (BPs) as recorded by an oscillometric BP monitoring system (Dinamap 1846) in premature newborns and advised cautious interpretation of the Dinamap BP readings in this age group. It is an interesting finding in the presence of a number of articles confirming the accuracy of Dinamap BP measurements in full-term neonates (references 2 through 7)1 and in infants and children aged 1 month through 16 years.2 In fact, we have found the Dinamap method to be a better predictor of intra-arterial BP than the conventional auscultatory readings obtained by research nurses.2 However, on close inspection of our data, we find a trend of diminished accuracy of the Dinamap readings when arterial pressures were in the low range, such as in diastolic pressure ranges. These findings raise the possibility that the Dinamap Monitor may be less accurate in the lowpressure ranges, such as are seen in premature infants.

With respect to the methods used by Wareham et al, however, there are two issues that need to be addressed. The first has to do with the way the Dinamap readings were compared with the direct arterial pressure. The authors took a direct arterial pressure reading from the monitor when a new oscillometric reading appeared and then compared the two for accuracy. It should be understood that, unlike auscultatory or ultrasonic devices, the Dinamap Monitor does not display its pressure readings at specified and known instants in time. Displayed Dinamap values reflect pressure values some time during the deflation cycle preceding the display; the deflation cycle may be of considerable duration. Therefore, a simultaneous reading is not possible with the Dinamap monitor. Some degree of BP fluctuation is always present and occurs to a greater degree in patients with respiratory distress or in those who require high respirator settings. Because of the unique nature of this device, Ramsey3 and the Association for the Advancement of Medical Instrumentation (1982) recommended the use of "range" of intra-arterial pressures to evaluate an oscillometric device. It is

highly recommended that a permanent recording of the pressure wave be obtained and that the highest and lowest values be determined. When the indirect pressure reading is within the range of direct arterial pressure readings, it is considered to be in perfect agreement. The difference between the indirect value and either the highest or lowest value is considered to be the degree of deviation. This method is discussed in detail elsewhere. 2,3 Thus, what the authors compared are not simultaneous direct and indirect BP readings.

The other issue concerns the accuracy of the direct arterial pressure reading. Although the intra-arterial pressure reading is considered the 'gold standard," it is so only when the direct pressure monitoring system meets certain standards. The fluidfilled catheter-transducer system is frequently unable to reproduce rapidly changing waveforms, and either overshoot or overdamping produces a higher or lower pressure reading. It is not uncommon that many BP monitors used in intensive care units, unlike those used in the cardiac catheterization laboratory or research laboratory, do not meet acceptable standards for direct arterial pressure measurement. It is important for the authors to specify what the natural frequency of the monitoring system was and what the damping coefficient was. Were these values within the acceptable range for accurate intra-arterial pressure measurement, such as that published by Gardner?4 Distortion of the waveform due to inappropriate natural frequency or damping coefficient, among other known factors, can falsely change the direct pressure readings. If these requirements are not met, the direct arterial pressure readings are not reliable, and readings from an indirect device should not be compared with unreliable standards. The authors should clarify these aspects.

MYUNG K. PARK, MD Department of Pediatrics University of Texas Health Science Center San Antonio, TX 78284

1. Wareham JA, Haugh LD, Yeager SB, et al: Prediction of arterial blood pressure in the premature neonate using the oscillometric method. AJDC 1987;141:1108-1110.

2. Park MK, Menard SM: Accuracy of blood pressure measurement by the Dinamap Monitor in infants and children. Pediatrics 1987;79: 907-914.

3. Ramsey M III: Noninvasive blood pressure

monitoring and validation, in Gravenstein JS, Newbower RS, Ream AK, et al (eds): Essential Noninvasive Monitoring in Anesthesia. New York, Grune & Stratton Inc, 1980, pp 37-51.

4. Gardner RM: Direct blood pressure measurement: Dynamic response requirements. An-esthesiology 1981;54:227-236.

In Reply.—Dr Park raises important issues relevant to the interpretation of oscillometric BP readings. It is true that the Dinamap Monitor derives values from analysis of multiple pulses waveforms during the inflation-deflation cycle. Since the precise period of sampling is unknown to the user, Dr Park argues that the highest and lowest BP encountered during the entire Dinamap cycle should be the appropriate range for comparison with intra-arterial BP recording. We agree that this would be a desirable method for the rigorous evaluation of an oscillometric device. However, it was our intention to examine the Dinamap Monitor as it is used in a clinical setting. We believe that most physicians would consider the oscillometric and direct arterial pressure values to be interchangeable and would make the same clinical decision regardless of the method employed. Consequently, we think that it is important to emphasize the occasionally large differences between oscillometric and direct arterial measurement. This discrepancy may, as Dr Park postulates, be due to BP variability during the Dinamap cycle, although this is not our clinical impression, or it may, in fact, be inherent in the oscillometric technique when employed in the premature infant. Investigation of the source of the discrepancy was not the subject of our study.

The intra-arterial BP monitoring system used (Transpac) had a natural frequency of 34.8 Hz and a damping coefficient of 0.20, both of which are within the acceptable range published by Gardner.1

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1. Gardner RM: Direct blood pressure measurement: Dynamic response Anesthesiology 1981;54:227-236. requirements.

Snoring, Daytime Sleepiness, and Sickle Cell Anemia

Sir.—Theoretically, in patients with sickle cell anemia who autosplenectomize by age 4 to 5 years a compensatory hyperplasia of other lymphoid organs may develop, particularly in the tonsils and adenoids. If so, symptoms associated with tonsillar hyperplasia should occur more often in patients with sickle cell disease than in normal children. Enlarged tonsils and adenoids are the most frequent cause of sleep apnea syndrome in pediatric patients.1 If tonsillar and adenoidal hypertrophy is more common in patients with sickle cell disease than in children without the disease, the symptoms of sleep apnea syndrome (eg, snoring and daytime sleepiness) should occur more frequently in them than in children without this disease. Since hypoxemia is poorly tolerated by patients with sickle cell anemia, sleep-related apnea in this population could produce much greater morbidity than in children with normal oxygen transport. In particular, sleep-related hypoxemia could possibly precipitate the various acute illnesses (painful crises, strokes, etc) associated with sickle cell disease.

A questionnaire was distributed to 58 parents of patients with sickle cell disease at the Comprehensive Sickle Cell Center of Detroit. Fifty-seven questionnaires were completed and returned. Patients' parents were asked about all of their children. They were asked to identify which children had sickle cell disease, which snored, and which seemed to be abnormally tired or sleepy. These questions were chosen because the literature suggests these are the most common symptoms of sleep apnea syndrome. The patients' siblings who did not have sickle cell disease served as controls for our anal-

Data were obtained for 167 individ-

uals; 65 were patients with sickle cell anemia (mean age, 8.9 ± 4.5 years), and 102 were siblings without the disease (mean age, 8.5 ± 4.6 years). The Table summarizes the questionnaire results.

Of the 102 controls, only 18 (18%) were snorers, but of 65 patients with sickle cell disease, 28 (43%) were snorers. Patients were significantly ($\chi^2 = 12.87$, df = 1, P < .001) more likely to snore than their siblings without sickle cell disease.

Daytime tiredness or sleepiness was reported both in patients with sickle cell disease and in controls but was much more common (18% vs 4%) in patients with sickle cell disease $(\chi^2 = 9.68, df = 1, P < .01)$. Since snoring is much more common in patients with sickle cell disease than in controls, one must wonder whether snoring or sickle cell disease is associated with daytime tiredness and sleepiness. We performed χ^2 tests looking at these symptoms as a function of snoring. Across groups, daytime tiredness or sleepiness was more likely in snorers than in nonsnorers ($\chi^2 = 9.97$, df = 1, P<.02) or subjects without sickle cell disease $(\chi^2 = 9.42, df = 1, P < .01)$. Within the total snoring population, there was no difference between patients with sickle cell disease and controls in the incidence of tiredness and sleepiness ($\chi^2 = 1.36$, df = 1, not significant).

The results of this study are as follows: (1) Children with sickle cell disease snore more and are more likely to be tired and sleepy than their siblings without sickle cell disease. (2) Children with or without sickle cell anemia who snore are more likely to be tired or sleepy than children who do not snore. (3) The association of daytime tiredness and sleepiness with snoring is stronger than the association with sickle cell disease. Therefore, the perceived tiredness or sleep-

iness of patients with sickle cell disease is more likely a consequence of a pathologic condition associated with snoring than with sickle cell anemia itself.

The symptoms of partial or complete upper airway obstruction during sleep are more common in children with sickle cell anemia than in their siblings. This has an obvious clinical impact in patients with sickle cell disease, whose tolerance of even mild hypoxemia is poor and in whom these symptoms are most common at the age of highest incidence of cerebrovascular accidents.2 Follow-up studies need to be done to find out whether children with these symptoms do or do not actually experience clinically significant airway obstruction and intermittent hypoxemia during sleep.

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1. Guilleminault C, Korobkin R, Winkle R: A review of 50 children with sleep apnea syndrome. Lung 1981;159:275-287.

 Mills ML: Life-threatening complications of sickle cell disease in children. JAMA 1985;254: 1487-1491.

Cape Malay Hypospadias/Mental Retardation Syndrome

Sin—The discovery of a new syndrome is always noteworthy. This is especially so when the syndrome is found first in an isolated community. A new syndrome of hypospadias, with mental retardation, is described in the November 1987 issue of AJDC. The excellent description is by Goldblatt et al from Cape Town, South Africa. Three brothers were affected by this syndrome, which includes microcephaly, craniofacial dysmorphism, lax joints, and beaked nails.

What gives this syndrome an extra dimension is its occurrence in the Cape Malay community, which is a social and religious isolate. More information about the Cape Malay community would be welcome, particularly with

| w.: | No. of Subjects | Subjects Reported to Feel Tired or Sleepy | Subjects Not Reported to Feel Tired or Sleepy |
|--|--------------------|--|--|
| Patients with sickle cell anemia | 65 | 12 | 53 |
| Snorers | 28 | 9 | 19 |
| Nonsnorers | 37 | 3 | 34 |
| Sibling controls | 102 | 4 | 98 |
| Snorers | 18 | 3 | 15 |
| Nonsnorers | 84 | 1 | 83 |

good references. References might include both general and those to genetic diseases found in the Cape Malay community. A map would help, too.

The genetic issue immediately at stake is whether this syndrome is inherited as an autosomal recessive trait or is X-linked. Occurrence of the syndrome in the Cape Malay isolate, of course, is consistent with a rare autosomal recessive trait, although, with three boys affected and no evidence of male-to-male transmission, this could be an X-linked recessive trait.

The pedigree of the Cape Malay family with hypospadias—mental retardation is limited to parents and children. The inclusion of matrilineal collateral relatives and earlier generations would be helpful to decide the likelihood of autosomal vs X-linked inheritance. How far back has the family been traced?

Since there is already a Goldblatt kidney, this new disease might best be called the Cape Malay hypospadiasmental retardation syndrome. This name is in keeping with that accorded by the authors and also gives the disease a distinctive name.

Whether the Cape Malay hypospadias-mental retardation syndrome is a private one confined to the Cape Malay community or is public and occurs elsewhere needs to be learned. In the meantime, the authors are to be congratulated on their clinical genetic acumen and pioneering report.

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1. Goldblatt J, Wallis C, Viljoen D: A new hypospadias-mental retardation syndrome in three brothers. *AJDC* 1987;141:1168-1169.

In Reply.—We are grateful for Dr Hecht's gracious comments concerning our description of a new syndrome of hypospadias with mental retardation.

The Cape Malay community is a socioreligious isolate estimated to number approximately 4000 individuals. The term Malay is a misnomer, as their origin is not the Malayan Archipelago. Their ancestors arrived at the Cape approximately three centuries ago from the Dutch East Indian islands of Sri Lanka and India. They are currently a small and endogamous community, distinguished by their ad-

herence to the Muslim faith. Owing to limited population size, only two exceptional genetic disorders have been reported from this community.^{1,2} They are also known to have a high incidence of diabetes mellitus, and the common genetic disorders are represented in their expected frequencies.

With regard to the genetic nature of this new disorder, no further light was shed by extensive family analysis. There were no other affected individuals in the extended kindred and no instance of overt consanguinity.

Finally, Dr Hecht's offer of eponymity is accepted with alacrity. Indeed, I am familiar with the Goldblatt kidney, but I can claim no social, professional, or genetic association with this esteemed researcher!

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1. Goldblatt J, Wallis C, Viljoen D: A new hypospadias-mental retardation syndrome in three brothers. AJDC 1987;141:1168-1169.

2. Viljoen D, Goldblatt JK, Wallis C, et al: Familial rhizomelic dysplasia: Phenotypic variation or homogeneity? Am J Med Genet 1987; 26:941-947.

Recognition of Coarctation of Aorta

Sir.—We read with interest the article by Thoele and colleagues1 relating their experience in the prereferral diagnosis of coarctation of the aorta (CoA). We agree with them that in the asymptomatic child, the most important reason for a lack of diagnosis is an incomplete physical examination. Several recommendations were made. Palpation of the peripheral pulses and measurement of blood pressures were the most important of these sugges-However, in our opinion, tions. misleading emphasis was placed on pressure palpation and blood measurement in the right arm, almost to the exclusion of palpation and measurement on both upper extremities. Although Thoele and colleagues are correct in emphasizing that a left subclavian artery arising near or distal to the site of coarctation is not uncommon, an aberrant right subclavian artery can and does occur in a similar fashion. We recently encountered a

child first referred at 51/2 years of age (the condition was correctly diagnosed by his pediatrician) with exactly this combination of findings. He was entirely asymptomatic, and the only physical sign suggestive of this diagnosis was a more prominent pulse in the left arm. Indeed, his blood pressures were "normal" and equal in the right arm and left leg (right arm, 104/ 80; left leg, 106/systolic) but in the hypertensive range in the left arm (138/60). Cardiac catheterization prior to surgical repair confirmed the clinical findings. The patient underwent uneventful repair of his CoA.

Although uncommon, aberrant origin of the right subclavian artery in combination with CoA does occur. To identify this subset of patients, we insist on palpation of pulses and blood pressure determinations in both arms and at least one leg.

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1. Thoele DG, Muster AJ, Paul MH: Recognition of coarctation of the aorta: A continuing challenge for the primary care physician. *AJDC* 1987;141:1201-1204.

In Reply.—The comments of Giroud and colleagues are a welcome addition to the list of diagnostic pitfalls in CoA and recommendations on how to avoid them. No one can disagree that a thorough clinical examination is preferable to a cursory one. We doubt, however, that blood pressure measurements in both upper extremities in all children will ever become an accepted routine. We therefore emphasize careful palpation of upper- and lower-extremity pulses and blood pressure measurement at least in the right upper extremity as a part of first-time examination of an asymptomatic child. In the case Giroud and colleagues report, the referring physician noticed the prominent pulse in the left arm and, as a result, made appropriate blood pressure measurements.

Aberrant origin of subclavian arteries makes the clinical presentation of CoA atypical and makes its recognition more difficult. Cases of "pulseless disease" due to aberrant origin of one or both subclavian arteries from the low-pressure aorta below the coarcta-

tion are rare, and we believe that recognition of CoA with atypical clinical presentation is not necessarily in the domain of primary care medicine. In many patients with typical CoA, the left subclavian artery is displaced from the transverse aortic arch to the aorta immediately proximal to the CoA, resulting in appreciably reduced pulse and blood pressure compared with those of the right upper extremity.

Finally, an unfortunate error was made in our original article. The sentence in the first line of column 2 on page 1202 should have read as follows: "The male-female ratio was 1.8 [not

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Association of Supernumerary Nipples and Renal Anomalies

Sir.—I read with interest the articles by Kenney et al1 and Hersh et al2 as well as the editorial by Hoyme,3 all of which were related to the association (or lack of association) between supernumerary nipples and renal anomalies. I would like to point out that Kenney et al misquoted an article by me and my colleagues4 on the same topic published in AJDC four years ago. Our population consisted of Israeli (not American) neonates, and we did perform renal ultrasound examinations (not solely physical examinations) in 11 neonates.

As Dr Hoyme pointed out, the study design was eminently different in the articles by Kenney et al and Hersh et al; in the former report, term neonates were studied; in the latter report, dysmorphic children. Both studies were conducted with American children, and the results were diametrically opposed.

I would like to draw a parallel between the results of these two studies and those reported by me and my colleagues4 and Varsano et al5 in an Israeli population. Again, the study design was different-routinely examined newborn infants vs children referred to an emergency room.5 The same difference in results was reported in the Israeli studies as in the American studies: no association with renal anomalies in our report vs a strong association in Varsano and colleagues report.

From the results of above studies, I concur with Dr Hoyme that the random finding of an isolated supernumerary nipple probably does not justify costly renal investigations. These investigations, however, seem to be justified whenever other clinical findings, such as urinary tract infection or multiple congenital anomalies, are present.

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1. Kenney RD, Flippo JL, Black EB: Supernumerary nipples and renal anomalies in neonates. AJDC 1987;141:987-988.

2. Hersh JH, Bloom AS, Cromer AO, et al: Does a supernumerary nipple/renal field defect exist? AJDC 1987;141:989-991.

3. Hovme HE: Minor malformations: Significant or insignificant? AJDC 1987;141:947.

4. Mimouni F, Merlob P, Reisner SH: Occurrence of supernumerary nipples in newborns. AJDC 1983;137:952-953.

5. Varsano IB, Jaber L, Garty BZ, et al: Urinary tract abnormalities in children with supernumerary nipples. Pediatrics 1984;73:103-

In Reply.—Through a typographical error, the study by Mimouni et al was not properly referenced in our introductory sentence. However, in the "Comment" section, we noted that his study subjects were newborn Israeli infants. We should have included an annotation that 11 of 43 newborns with supernumerary nipples in Mimouni and colleagues' study also had a renal ultrasound examination.

We appreciate Dr Mimouni's careful reading of our article and his concurrence that supernumerary nipples alone in black children¹ do not warrant an investigation for a hidden renal anomaly.

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1. Robertson A, Sale P, Sathyanarayan: Lack of association of supernumerary nipples with renal anomalies in black infants. J Pediatr 1986:109:502-503.

In Reply.—Dr Mimouni highlights two important points that I and my colleagues addressed in our report: (1) He indicates that there is no need to perform renal ultrasonography if a supernumerary nipple is identified in an otherwise normal individual without a history of urinary tract problems. (2) He believes that the presence of a supernumerary nipple in an infant or child with multiple congenital anomalies is an indication for an ultrasound examination of the kidneys. In his editorial, Dr Hoyme agreed with this approach.

Recently, a follow-up study from Hungary' again demonstrated an increased incidence of renal malformations in infants and children with a supernumerary nipple who were otherwise normal. Renal abnormalities were found in six (8%) of 78 patients hospitalized for illnesses unrelated to the urinary tract and healthy newborn infants; the authors believed this reinforced the original recommendation by Méhes² to perform roentgenographic studies of the kidneys in this patient population. Although the reason for this discrepancy in Hungarian children is unknown, I consider the recommendation made by us. Mimouni, and Hoyme for a normal individual with a supernumerary nipple to be appropriate in the United States. Further studies will be required among different patient populations to determine if the results obtained by Méhes^{2,3} apply elsewhere.

Based on Mimouni's recommendation for individuals with multiple congenital anomalies found to have a supernumerary nipple, it is uncertain whether he also intended to include those with minor anomalies. As we pointed out, the presence of additional minor anomalies may represent a higher risk for the presence of renal malformations. In fact, Meggyessy and Méhes¹ found that two (33%) of six patients with dysmorphic signs or malformations had renal defects. I agree with Dr Hoyme. Children with a pattern of multiple anomalies, including both major or minor ones, who have a supernumerary nipple should undergo additional renal investigation.

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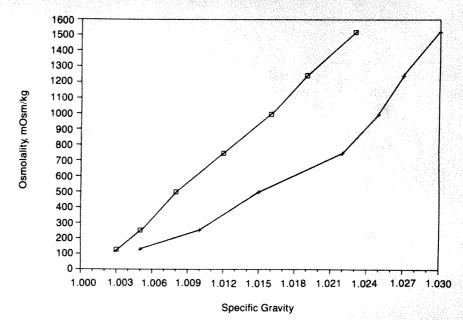
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Interpretation of Specific Gravity by Dipstick

Sin—The widespread use of dipsticks such as the Ames N-Multistix-SG strip (Miles Laboratories, Elkhart, Ind) has some built-in problems as well as a form of medical laboratory absurdity. Comments have been made in the more general literature, but to date we have not read a comment in a pediatric journal.

I refer specifically to the use of the term specific gravity that one reads from these strips. The measurement of specific gravity in urine has been used in clinical medicine for a number of years with known advantages and disadvantages. One advantage is that in the absence of albumin and glucose, the specific gravity has a nearly linear correspondence to osmolality over the range of interest to the clinician. This correlation enables one to detect the ability of the kidney to concentrate and dilute, which is a sensitive measure of renal function. This usefulness is lost if there is significant albumin, glucose, or foreign substances, such as radiopaque contrast material, in the urine.1 Another advantage is that a high specific gravity points to the presence of albuminuria or glycosuria.

The dipstick measure is sensitive to the ionic strength of the urine, giving a linear correspondence to osmolality contributed by electrolytes. Since that contributed by urea (and not detected by the strip) generally parallels the contribution of electrolytes, one could say that the dipstick measures more precisely the renal function that is really wanted, namely, osmolality. By calling the measurement specific gravity and calibrating it as such, the company gives a different number for specific gravity than that obtained



Comparison of refractometer specific gravity and "SG" readings for sodium chloride solutions of known osmolality. Squares indicate refractometer readings of specific gravity, while plus signs indicate Ames N-Multistix-SG (Miles Laboratories, Elkhart, Ind) dip strip readings of SG, ie, the company's interpretation of specific gravity.

with a hydrometer and runs the risk of completely befuddling the user.

The determination does not measure albumin and glucose, though this does not present a problem since the same strip will pick up these two substances with separate spots. The chemical mechanism by which the strip works is to provide a polyionic polymer with binding sites saturated with hydrogen ions that are preferentially replaced by cations (eg, sodium or potassium cations); the color change is an indicator of pH affected by the released hydrogen ions.³

The complaint then regards the type of calibration called "SG" giving numbers that, for older clinicians particularly, will not correspond to their previous experience. The company should calibrate the determination as osmolality, recognizing that it is a surrogate producing an approximation, which is

true in any event. Meanwhile, those using the strips had best be aware of what is really being measured. The Figure illustrates SG readings by refractometer and dip strip for sodium chloride solutions of known osmolality.

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CORRECTION

Incorrect Ratio.—In the article titled "Recognition of Coarctation of the Aorta: A Continuing Challenge for the Primary Care Physician," published in the November issue of *AJDC* (1987;141:1201-1204), a sentence contained an incorrect ratio. On page 1202, the first sentence in column 2 should have read as follows: "The male-female ratio was 1.8 [not 1:8]."

Editorials

Trauma and Toxins

The Linkage

That "coming out" party of the Division of Injury Epidemiology and Control at the Centers for Disease Control, Atlanta, as Vernon N. Houk, MD, Stuart T. Brown, MD, and Mark L. Rosenberg, MD, expressed it at last year's Conference on Injury in America, heralds a quantum advance in the management of today's major public health problem. Looking upon injuries as a disease, and not as "accidents," helps laymen and professionals alike gain a better understanding of the numerous hosts, agents, and environments involved in the many facets of this disease.

With only a few "passive" measures available (those built-in safety features in products and environments, in contrast to "active" measures involving behavior change, however, to contain certain damaging energy releases, we face a formidable task in coping with that multitude of other hazards for which no "safe-proof" modalities are available and to which young children are exposed at such great risk.

The daunting problem facing health care professionals in the United States, as well as parents and all persons concerned with children's wellbeing, is how best to improve our abysmal record with respect to death rates from childhood injuries, poisonings, and violence, compared with rates in other industrialized countries.

Hearty applause should also be accorded the new name of this injuryconcentration in Atlanta. Implicit in the title "Center for Environmental Health and Injury Control" is recognition of the close relationship between environmental hazards and trauma of many types.

Where I think that an injury-environmental relationship should be made especially strong and binding is between two committees of the American Academy of Pediatrics (AAP). With the name of the Accident Prevention Committee soon to be changed to the Injury Prevention Committee, I trust, would it not be logical to meld this committee with the Environmental Hazards Committee? The bulk and perhaps the worst of the problems to which these two committees of the AAP direct their efforts, be they labeled injuries or environmental hazards, coexist in and around the home, and getting to and from them and daycare centers, and schools where children spend most of their time.

Just as injuries were referred to not long ago as the "new morbidity," and are now formally classified as a disease, so the pathologic disorders created by environmental toxins can be thought of as the newer morbidity. True, the impact from these toxins is not as immediately obvious as that produced by the traumatogens; however, the neurotoxins, carcinogens, mutagens, teratogens, and immunosuppressants—that formidable list of pollutants in the air we breathe, the water we drink, the foods we eat, and, frequently, the soil under us-are exacting a toll, and the toll is generally heavier on young developing organisms than on healthy adults, although standards are set for what the latter (not the former) can tolerate.

The tip of the iceberg is represented by the well-documented hazards of low levels of lead, cigarette smoke, and combustion products. Lurking below are equally, if not perhaps even more, insidious threats to young organisms from asbestos, radon, and pesticides.

In concentrating on children's cognitive limitations with respect to the dangers that confront them in 20thcentury America, we may forget these children's biologic limitations. For example, regardless of the point of entry of a toxin—through the respiratory tract, gastrointestinal tract, or skinchildren are at considerably greater risk than are their fathers and mothers. Children breathe faster, and thus inhale more toxins. In addition, the small particulates (which may be the most deleterious) can penetrate deeper into children's respiratory tracts. Also, children eat and drink more per unit of body weight than do adults, and thus ingest and imbibe more toxins. Transdermally, children's thinner skin permits easier penetration of toxins.

We need to remind ourselves of such important facts as these: for a 5- to 10-year-old child, the cancer risk from asbestos is said to be ten times greater than for a 35- to 40-year-old adulti; children are five to ten times more vulnerable than adults to radiation damage, with the risk being two to three times greater for children under 10 years of age; and children are at a disadvantage two to nine times greater than are adults with respect to pesticide exposure. Even though we are cognizant of young children's greater sensitivity to lead, one must bear in mind that—at the same level of airborne lead-children's blood lead concentrations are several times higher than adults'.

Indoors, there is a closer relationship between the traumatogens and toxins than may at first be apparent. Think of it this way: a preschool child can choke on peanuts, but, if enough of them have been consumed before such an episode, the child will be exposed to the carcinogens and neurotoxins from the pesticide residues that many nuts (as well as a number of other foods) contain. Again, a toddler can suffer a burn from a wood stove, while at the same time inhaling the toxic combustion products the burning wood releases. At school, a child can hit his or her head by falling down on a concrete-paved playground; before the accident the child may have been exposed indoors to friable asbestos and perhaps radon.

We have child-resistant containers for dangerous medications, and they have had a major impact (as most everyone realizes) on reducing mortality and morbidity from toxin ingestion. If only we could so easily and successfully design a cap for the noxious airborne pollutants found in such heavy concentrations in many indoor environments! Before we achieve such a "technical fix" however, we can do a great deal to limit children's exposure to deleterious pollutants by improving the quality of indoor air. (In many instances, this quality has been found to be far worse than that of outdoor air.) Fortunately, as the Conservation Foundation² points out, "control measures [for indoor air] tend to be inexpensive.'

The hazards-prevention opportunities facing child care professionals, and especially pediatricians, today are mind-boggling. First, besides alerting their own patients to the importance of anticipatory guidance by means of the AAP's Injury Prevention Program, how much time and energy can busy practicing clinicians devote to the larger community? If clinicians are motivated to extend their efforts, then a determination must be made as to how and where, and toward whom, that time and energy should be directed. Should family or larger group sessions, physicians' offices, well-child clinics, daycare centers, and schools all be included? How can the input be maximized? Is dispensing specific information on one hazard at a time preferable and most cost-effective? Or against several of the most hazardous agents? Or those hazards most prevalent in a specific community? What percentage of time and energy should be allocated solely to improving caretakers' behavior? To children's behavior? To the need to pressure for improved product designs and environments?

There are no quick and easy answers emerging from the growing body of literature describing injury-prevention programs involving numerous intervention strategies and communications methods. Today's conventional wisdom favors community-level group efforts aimed at providing selected "how-to" prevention information embodying several components, including education, technology, and government.

Some pediatricians prefer the legal advocacy route. We certainly need better enforcement of existing regulations for a number of problems, including smoke detectors, fire extinguishers, and crumbling lead paint, to name just a few. We also need professional input in the form of expert testimony before regulatory commissions, not only for noncompliance, but for new regulations such as for helmets for bicycle riders, for removal of rigid poles on highways to reduce injuries from motor vehicle collisions, and for the cleanup (not just the reporting) of friable asbestos in schools.

Coalition building is another useful approach to further the cause of prevention by increasing public awareness and political clout. Since fatalities among child pedestrians occur approximately as frequently as they do among children riding as passengers in cars (for which we have a technical fix, if only it was used routinely and properly), I would like to suggest the formation of a Child Pedestrian Safety Association headed by health care pro-

fessionals and including Parent-Teacher Association groups, city planners, and concerned others. With drowning as the second leading cause of death (not including the large number of near-drowning cases) among children between 5 and 14 years of age, and with 2-year-old children at especially high risk, a valuable contribution could be made by a Child Pool Safety Group that included a coalition of health care workers along with manufacturers. swimming pool YMCAs, YWCAs, and others. Again, Campaign Against Children's Toxins, together with environmental and human ecology organizations, could help to acquaint nonprofessionals with children's unique sensitivities and press for air-, water-, and foodquality standards that can safely be tolerated by the young subset of our population.

Pediatricians should never forget how tall they stand in the public eye as children's special guardians, how much influence they can exert "pro bono kids," and how such influence represents a veritable sine qua non for mitigating the largely preventable ravages of both the new and newer morbidities. Besides the humaneness of it all, let us not forget that such efforts will assuredly prove to be costeffective.

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Ipecac

When Prevention Fails

The American Association of Poison Control Centers reports that 80% of all poisonings occur via ingestions.1 Emesis induced by ipecac is the most efficient, rapid method to empty the stomach.2 Experience demonstrates that active methodologies to reduce the incidence of toxin ingestions, such as repeated counseling of the caretaker, have had poor success rates.3 They require frequent education, which is generally not provided, accepted, or remembered.

See also pp 596 and 640.

Passive interventions are significantly more successful. The primary need is to promptly, efficiently, and safely remove the toxin from the gastrointestinal tract. The mean time from ingestion of ipecac to emesis is 20 minutes (this can be shortened by appropriately increasing the dose). This is significantly less time than it takes to bring the child to an emergency room or for the caretaker to obtain ipecac from a secondary source outside the home (assuming that transportation, funds, and a source are available).

Assessment of the risk of misuse of ipecac in the home has not been well quantified. Chafee-Bahamon et al4 concluded that the adverse side effects are mild and that the benefits far outweigh the risks.

Contraindications include the unconscious child, the convulsing patient, those who have ingested caustic substances, children less than 6 months of age. The list of contraindications may be known by the provider, but there should be no hesitancy in obtaining further advice from the regional poison control center.

Education of the physician and the pharmacist about making ipecac available is necessary. This is not simply accomplished. Malloy and Rhoads⁵ point out the low incidence of caretakers who keep ipecac in the home (9% to 25%). This probably reflects how infrequently poison control is discussed during the well-child visit. I suspect that most ipecac for prophylaxis is dispensed after the patient has had at least one episode of ingestion of a harmful substance. I prefer the physician to be the primary source, because he or she may be more authoritative and because this eliminates the need for the parent to go to a secondary setting. Any individual who dispenses ipecac is obligated to educate and properly label the bottle. Some caretakers, because of poor parenting skills or communication difficulties, are not candidates for keeping ipecac in the home.

The label on the bottle should primarily instruct of the need to contact an authoritative source that is readily available 24 hours a day. Telephone numbers should be included. It is unacceptable, however, for callers to be placed on hold for long periods of time, since the caretaker may proceed without proper instruction.

Additionally, an easily understood accompanying instruction sheet that includes the most common poisons should be made available. This should list the contraindications in lay terms, such as camphor and furniture polish as opposed to petroleum distillates. Warnings should include the caveat that the antidotes listed on products are frequently wrong. These instruction sheets and labels for ipecac bottles must be standardized by an appropriate agency or organization. A note should be made on the patient's chart that ipecae and instructions have been provided. Subsequently, if the patient does ingest a toxin and ipecac is prescribed, further documentation should be included in the patient's chart. This latter suggestion is made in an effort to prevent any malpractice litigation.

In these days of "marketing," this service should be a "natural." The name of the physician, pharmacist, or hospital would appear on the bottle and on the instruction sheet as further evidence of the individual's or organization's concern for the well-being of the child.

The use of ipecac is associated with a long and outstanding safety record. It can reduce morbidity and mortality. It may eliminate needless visits to an emergency setting.

Our colleagues must use a modified "Willy Sutton" rule and go where the money is.

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The Case for Ipecac Syrup

Methods of gastric decontamination have generated controversy among physicians treating toxin-related emergencies. A number of methods of decontamination exist, including induced emesis (by ipecac syrup, mild detergents, or apomorphine), nasogastric or orogastric lavage, and oral activated charcoal. No distinct advantages in effectiveness have been attributed to any of these methods in particular.

See also pp 595 and 640.

Charcoal is currently experiencing a resurgence of support in some publications1 and has been suggested by some authors as a replacement for emesis as a method of decontamination for nonacute poisonings. This may contribute to confusion by some practitioners and consumers who are concerned about the appropriate role of emesis in the management of poisoned patients. In some situations the characteristics of activated charcoal may make it the most appropriate mode of decontamination. Intoxication with a substance that has a rapid onset of toxicity and for which emesis would be contraindicated and lavage would be difficult or inappropriate, such as camphor, may be effectively treated with oral activated charcoal. In many other circumstances ipecac syrup remains an appropriate choice.

A study of activated charcoal in the home2 demonstrated that young patients are unwilling to take activated charcoal orally. In the office or emergency department this commits the practitioner to the added trauma of gastric intubation. This refusal also limits charcoal in its current forms as a useful home decontamination agent because it may be difficult to mix; it is messy and may stain furniture, carpeting, or clothing; and it is unpalatable, making it difficult for parents to administer in an emergency. In the emergency department the acute ingestions requiring aggressive intervention may justify the risks of nasogastric or orogastric intubation. In these situations the slow onset and prolonged duration of action of ipecac syrup may limit its usefulness. These concerns are appropriate, of course, and it is important that all physicians be aware of the limitations of induced emesis. Drugs that produce a rapid change in the level of consciousness, and substances that are corrosive to upper gastrointestinal tract should not be removed by induced emesis. Low-viscosity hydrocarbons remain controversial because of their aspiration risk with lavage or emesis. The large bulk of pediatric patients with an ingested substance do not fall into these categories. Among the roughly 1 million calls to the major poison centers of the United States in 1986,3 75% of cases were managed in the home. There remains, therefore, a need for an agent that can be used in the home for the management of nonsevere poisonings under the guidance of poison control center personnel or private physicians.

From the perspective of the poison control center, ipecac syrup is still a viable therapeutic modality. Data contributed by 57 poison control centers in 1986 reported 145 000 cases in which ipecac syrup was the primary form of decontamination. Among these cases, 55% of decontaminations occurred at home. Without the availability of syrup of ipecac this would have meant an additional 80 000 visits to health care facilities. This represents the tip of the iceberg with respect to the use of ipecac but underscores the need for this product if poison control centers and pediatricians are to continue to manage nonsevere ingestions in the home.

Based on the above reasoning, we feel there is a continuing need for ipecac syrup in the home as an adjunct to the management of nonsevere poisonings. Our educational emphasis should be on the supervision of the use of ipecac syrup by a physician or personnel of a poison control center. This should include cautions about the potential for abuse of this substance by

patients with eating disorders. The pediatrician should also be aware of the potential for "Munchausen-byproxy" syndrome from parental misuse of this substance. Given the widespread distribution of ipecac syrup, the low incidence of these problems underscores the overall safety of this product. Parenthetically, the most recent package insert for Actidose With Sorbitol, a common oral activated charcoal preparation, strongly advises that this preparation not be used in children weighing less than 16 kg because of the possible adverse cathartic effects of sorbitol.

Based on the article by Malloy and Rhoads in this issue of AJDC, it is apparent that the perceived need for ipecac is not being met by current methods of distribution. Thus, it is our feeling that ipecac syrup should be distributed as part of well-baby care with information on the appropriate use of this product and the telephone numbers of the primary physicians and the local poison control center. In this way we can preserve an important mode of home management for both physicians and poison control centers.

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Acute Supraglottitis (Epiglottitis): To Look or Not?

In this issue of AJDC, Mauro et al have presented some challenging data. This study reports their observations on direct examination of the epiglottis in sequential fashion, taking care not to touch the epiglottis, nor to visualize the glottis, in children presenting with acute stridor. The review of this report by expert referees, members of the editorial board, ad hoc consultants, and the chief editor resulted in divergent opinions on the safety of the methods used, the actual numbers of children involved, the rate of complications, the potential "danger" if this method were applied across a broader spectrum of children with stridor, and the adequacy of follow-up.

See also p 679.

I originally rejected this report on the basis of potential "danger" and on the variable assessments, from which I could not gain a clear consensus for acceptance. The authors responded, in spirited but logical fashion, requesting that the decision be reconsidered in the light of the actual experience that they had reported and not on the potential for misunderstanding.

In my view, they successfully countered each of the objections raised with logical, considered reasoning. In the end, I reversed my original decision, largely based on the total analysis and on the request by the authors that we let "the readers decide."

Conventional dogma, which I and countless others have repeated for decades now, is that children for whom the diagnosis of supraglottitis is considered should not have the epiglottis inspected for fear of a vasovagal response that would result in immediate and irreversible cardiorespiratory collapse, respiratory obstruction, and death. In fact, in many of our practices, we have encountered children who,

having been exposed to oropharyngeal manipulation, have died with the diagnosis of supraglottitis made at the autopsy table. However, the authors of this article did not just manipulate the oropharynx in careless fashion; rather they prescribe a sequential method of examination by each of the following four methods: light alone with the child opening the mouth; light and wooden tongue depressor, with the child in a sitting position; direct pharyngoscopy with the child sitting; and, finally, laryngoscopic inspection, with the child supine. In those anecdotal instances of oropharyngeal manipulation, we do not know what method was used and to what degree a traumatic approach in a struggling or restrained child was employed. In addition, the current study was conducted in an emergency room setting, with an anesthesiologist immediately available.

The authors note the paucity of literature on the safety of direct inspection and the inadequacy of the data contained in the extant reports, which are few. There are a few articles that indicate that direct inspection is safe, but these suffer the same deficiencies as those that report airway obstruction. Why then does the present report differ from common wisdom and accepted dogma? First, it is possible that the series of 155 children, with only six having definitive diagnoses of supraglottitis, is insufficient to "prove" that even the authors' careful method is safe for all children. Several reviewers were concerned with this issue, ie, might the seventh child have suffered obstruction or collapse? Second, it is possible that the authors are correct and that their method, carried out in the presence of an experienced anesthesiologist, although performed by a diverse group of residents and pediatricians, is safe.

Another issue raised was the lack of diagnosis of bacterial tracheitis in this group of 155 children. The authors indicate that no indication for subglottic inspection was displayed by these children, hence the ultimate diagnostic criterion could not be tested. This implies, but does not prove, that bacterial tracheitis simply did not occur in this sample.

Some were concerned that true supraglottitis might have been overlooked in this sample. However, the authors were able to contact all of their patients from seven to 21 days after entry into the study, and in no instance did any evidence present that suggested that supraglottitis was missed.

We are left then with the actual results of the study and the methods used to obtain them. We urge you to read the report carefully and, if you agree, or disagree, let us know by letters for possible inclusion in the PEDIATRIC FORUM. In practice, this issue is an important one. Most pediatricians with whom we are familiar would not attempt inspection of the oropharynx in a child for whom they suspect the presence of inflamed supraglottic structures. Are they, and the consultants, such as me, correct in this view? Or are the authors correct in suggesting that the method used can permit safe inspection of the epiglottis, even if the child has supraglottitis? Let us know what you think.

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PhD Faculty in Pediatric Departments

Traditionally, the idealized image of the academician combines the clinical acumen of an Osler, the teaching charisma of a Socrates, and the de novo thinking of an Einstein. More recent realities have made it painfully apparent to most chairs of pediatric departments that the "triple threat" physician/academician is, at best, a rarity. Despite this new "academic morbidity," the chair is expected by deans, boards of trustees or regents. and legislators not only to manage patients well but also to teach the next generation of physicians and generate new knowledge in the process. Although the successes with which this goal can be reached are variable, all those who try have to make certain that financial ends meet if their departments are to survive. Since the halcyon days of more plentiful federal research funding of the 1960s have passed, it is painfully apparent that innovative and unique ways are needed to keep the teaching and research components of an academic department intact.

See also pp 599 and 675.

The survey by Leuschen et al in this issue of AJDC begins to probe one possible solution to building a department of pediatrics in the modern medical world. The authors accomplish this by gathering information from 92 chairs of pediatrics regarding the numbers and demography of PhD faculty in their departments. They conclude that PhD faculty may impact significantly on the long-range plans of a department. Although I strongly agree, there are a host of questions that need to be addressed before solutions are found that are applicable in any given situation.

A major, sustained commitment to research must be established before a chair hires PhD faculty and expends departmental resources in so doing. The PhD faculty member cannot generate revenue from patient care (with some exceptions, eg, clinical psychologists) and can become a financial burden to the department unless they are successful in obtaining release-

time salary from sponsored project support. Incidentally, when one looks at efficient means for generating salary support, release time from grants is the best way to accomplish this goal. To hire and retain the talented PhD faculty member, one needs to offer a long-term commitment, usually in the form of a tenure-accruing appointment. If in the course of time, after tenure has been achieved, success in obtaining grants falters, the department is, nevertheless, committed to a faculty member who does not have a "fallback" source of support (eg, patient billing). In the interval from 1971-1972 to 1982-1983, the reliance on patient care revenue has increased from 12.2% of total medical school operating budgets to 32.1%. There is no reason to believe this trend will reverse; in fact, it may increase in the future. Thus, departments that decide to build research productivity on PhD faculty members must be aware that a potential financial burden may await them in the future. However, the increasing reliance on clinical income also points out that departments with commitments to increasing their research profile and productivity probably must rely, to a major extent, on faculty capable of devoting the majority of their time to research, ie, PhD faculty. The MD faculty members should share in this decision making, as they will be responsible for bearing the brunt of the cost in the future.

In addition to departmental commitment, the medical school must permit clinical departments to build research efforts through the hiring of PhD faculty. How does the dean of a medical college respond to the chairperson in biochemistry who requests an additional faculty member to round out a departmental program, when the dean recognizes that the pediatric department has been granted a position for a PhD faculty member to accomplish the same program objectives? For example, both chairs might wish to hire someone with molecular genetics interests. Conversely, what happens if the reverse is true, ie, that the biochemistry department obtains the new PhD position and the pediatric department is denied their request for a similar person?

The dilemma centers around the principle of allowing a department to hire a specialist whose disciplinary affiliation is traditionally in another department's area, eg, in the case cited, hiring a biochemist in the department of pediatrics. The dean often cannot prevent controversial interdepartmental appointments but should solicit the support and advice of both chairs for a nontraditional appointment of a PhD faculty member in a clinical department. Such consultation should be prospective and should take into account the impact on both departments' research, teaching, and other programmatic activities. I suggest that the dean makes certain that the potential conflicts are understood by both chairs and that the search committees formed for recruiting such individuals have representatives from the relevant clinical and basic science departments.

Leuschen et al¹ have accomplished what PhD faculty in academic departments should, ie, generate and disseminate new knowledge. It is hoped that their report will stimulate deans and chairpersons to consider the efficiency of increased research productivity by the appointment of PhD faculty in clinical departments, in the present case, departments of pediatrics. Such appointment should be judiciously considered, with long-range programmatic and fiscal planning taken into account, and involve the advice and consent of all interested parties in a given medical school.

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Another View of PhD Faculty in Clinical Departments

In this issue of AJDC, we publish an interesting survey by Leuschen et al¹ and an editorial comment by Grant Morrow,² who is currently chair of the department of pediatrics at Ohio State University, Columbus. Both deal with the vexing problem of the appointment of PhD faculty in clinical departments, in this instance, departments of pediatrics. I would like to add a "dean's viewpoint," as this issue is encountered repeatedly in colleges of medicine, both in concept and in practice.

See also pp 598 and 675.

Colleges of medicine are confronted today with issues that never arose before, conditioned by the rapidly changing medical and research milieu, and complicated by the basic requirement that teaching of medical students, graduate students, resident physicians, and fellows underlies all of the college's activities. The immediate issue is the blurring of disciplinary lines and titles in assigning faculty positions to departments and the appointment of individual faculty whose disciplines differ from the primary one of the department in question. Ancillary issues that arise at the college level include, but are not limited to, salary levels between PhD faculty in clinical departments and those in the department of that PhD faculty member's primary discipline; initial appointment track (ie, tenure eligible or non-tenure eligible); criteria for academic progression; the college's commitment to such faculty in terms of space, research funding, and related resource issues; and interdisciplinary and intradisciplinary relationships in the institution.

The need for research-oriented faculty in clinical departments has been well outlined and discussed by Dr Morrow. Emphasis must be given to the sometimes impossible task for departments to develop an academic profile in keeping with institutional, and

their own, disciplinary objectives. Colleges, and the universities in which they exist, rightfully insist on acquisition of new knowledge as one of the primary goals for faculty and departments. This attitude dictates the allocation of resources, the development of the mission, objectives and goals of the institution and its constituent colleges and departments, and the award of tenure and the very stability of the department chairship. Basic science departments generally do not have difficulty in aspiring, and reaching, this goal of productive research. Clinical departments, because of the demands placed on them, have greater difficulty, unless they choose not to develop their teaching and clinical activities to the degree demanded by the needs of students and patients. Some departments may choose to have rather routine teaching programs, with heavy emphasis on resident-physician teaching, little demand placed on full-time faculty, and little reward offered to faculty for creative, and time-consuming, teaching effort. Similarly, clinical practice may be limited and selective, with emphasis on specialty care, especially in areas of highincome generation per unit of clinical effort. Departments with this profile can then afford to have clinical (MD) faculty members who conduct research and are productive. However, in today's economic milieu, such profiles are becoming almost impossible to achieve, given the inflation in faculty salaries and the reduction in research funding, which translates into the need for generation of large amounts of clinical income to enable both salaries to be met and excess income to be diverted into research effort. Furthermore, organized medical care systems adopted by some colleges for their clinical faculty have resulted in inability to select patient care activities, with an abundance of patients whose care must be provided. These trends tend to limit the clinician's ability to devote "thinking" time to research, let alone actual hands-on participation in traditional laboratorybased investigation.

As can be seen by the Leuschen et al1 survey, a significant number of PhD faculty members have been employed by pediatric departments in this country. This overall figure of 14.5% tends to obscure the geographic and size distribution also noted by these authors in their survey. Large departments, especially in California, the Midwest, and the central portion of the United States, tended to have a higher proportion of PhDs than did smaller departments elsewhere, especially on the Eastern Seaboard. One wonders if local factors, such as those enumerated above, play a larger role in these areas, and in larger departments, than they do elsewhere. Certainly, the health maintenance organization movement has greater impetus in the areas of high PhD activity, suggesting that those departments may have to have their clinical faculty more active in patient care, hence the greater need for PhD support for research activity. There may be other, more subtle influences at work, and further information would be useful.

The salary level paid to PhD faculty was not explored in this survey. In some institutions there is a discrepancy between the basic scientist appointed to a clinical department and to similarly trained and credentialed faculty in the "core" department. This discrepancy may result simply from the greater flexibility in resources available to clinical departments, but on the other hand may be attributable to an increased effort level by the PhD faculty member in a clinical department, longer hours, involvement in departmental committees that go beyond those normally extant in basic science departments, and like effort. Whatever the reasons, the discrepancy does have the potential for dissatisfaction among those paid less and for "seduction" by the clinical position, in competition with a position in the corresponding basic science department.

The initial appointment also raises institutional concerns. As discussed in the Leuschen et al1 report, various means are used to title PhD faculty members with "regular" tenure track appointments and various non-tenure eligible appointments. In regard to the tenure track, issues of appropriateness of the criteria used by the clinical department are raised, usually by the corresponding basic science department. On occasion, the basic scientists may feel that the criteria for appointment are "softer" for clinical PhD faculty appointments than for those applied in their own departments, ie, the implication that the person selected would never have been appointed in the department of their primary discipline.

If a non-tenure track appointment is made, then some basic scientists may claim that their counterparts in clinical departments are not being treated fairly and equitably by the clinical department. The use of adjectival professorial appointments (eg. research or clinical) may also be seen by others as a means of avoiding the more "rigorous" criteria necessary for a tenure track appointment. However, if an institution has a limit or quota on the number of tenure track appointments that may be made, the use of the non-tenure tracks may be the only way that additions to faculty can occur. Furthermore, the non-tenure track appointee usually does not have the same "guarantee" that tenure implies, ie, virtually professional life-long commitment, and, as discussed by Dr Morrow, the problem of continuing funding need not arise in the future if the resources necessary to support the PhD faculty member become unavailable. Obviously, this raises the issue of unfair treatment for such faculty, since their appointment is contingent on their ability to generate salary support and reflects no commitment on the part of the institution. These considerations argue strongly for an institutional position on such appointments, with clear understanding of all parties as to the direction, sustenance, and stability of the final arrangements that are made.

The criteria for academic progression must not differ for clinical departmental PhD faculty from those in their parent discipline. To allow for differing criteria, either softer or harsher, would foster differential value placed on such appointments. In either direction, the discrepancy would lead to potential isolation of the faculty member from the core discipline, and, therefore, isolation from the necessary collegiality and nurture so necessary in research endeavor.

Many colleges and universities allocate resources, either solely or preferentially, to tenure track faculty. If the PhD faculty member is not in the tenure track, denial of resources at the institutional level may prevail. The Leuschen et al1 survey indicated that "there is a substantial degree of flexibility" within professorial ranks, suggesting that non-tenure track appointments may be common. In addition to space and dollar allocation, the ability of non-tenure track PhD faculty to teach graduate students, to sit on graduate committees, and to be principals in various graduate educational activities, can be severely limited. In many colleges of medicine, other privileges are not afforded nontenure track faculty, such as voting rights. These inequities must be carefully weighed when the appropriate appointment is initiated.

Perhaps one of the most difficult issues is the collegiality of the faculty member, ie, the particular scientific associations and collaborations that develop stemming from the location of the departmental appointment. Is a biochemist in a pediatric department considered to be a biochemist in affiliations or a pediatric biochemist? What is the reception received by that faculty member in the department to which discipline he belongs? Does he give seminars in that department? Does he participate in faculty meetings? Indeed, does he have a crossappointment or is he considered a pariah? Conversely, what are the relationships between the PhD faculty member and the pediatric clinical faculty? Is he accorded equal voice and status on issues of departmental policy, departmental finances, and other issues not directly relevant to his research activities? And what of his teaching role? Does he teach in the basic science course, in the pediatric department, or at all?

The issues discussed above are not trivial and, with the seeming increase in PhD faculty in pediatric departments, will have to be faced by more and more colleges as time goes on. By exposition of the issues, I do not mean to imply that PhD faculty should not be appointed to clinical departments. I believe firmly that such development is essential to collaborative research efforts and can result in productive and creative activity of academicians in the medical college setting. My plea is to have realistic expectations and that careful planning precede such appointments. Ad hoc solutions can result in later confrontation, confrontations that could have been avoided had planning occurred. One very satisfactory solution, used in my current institution, is to develop joint planning, joint recruiting, and joint funding for as many PhD appointments in clinical departments as are possible. The collaborative nature of these steps results in the prospect for collaborative research, teaching, and, in some instances, service activities between the department of the primary appointment and that of the basic science discipline. Expansion of basic science research is allowed, and facilitation of clinical departmental research is fostered. Funding difficulties are eased by the contribution of the clinical department to the PhD faculty member's salary and difficult space allocation is often resolved by use of laboratory research space allocated or developed by the clinical department but unavailable to the basic science department. Such collegial solutions provide the best answer to what might otherwise be a knotty, unsolvable, and contentious situation.

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Leads From the MMWR

Morbidity and Mortality Report Centers for Disease Control, Atlanta

Case of Paralytic Illness Associated With Enterovirus 71 Infection

Feb 26, 1988 (Vol. 37, No. 7)—ON OCTOBER 1, 1987, an 18-month-old child was admitted to a medical center in central Mississippi 2 days after the onset of severe weakness in his left leg. On September 22, 1987, the child had received measles/mumps/rubella (MMR) vaccine in his right thigh and diphtheria/pertussis/tetanus vaccine in his left thigh. Five days after his vaccinations, his mother noted a temperature of 39.3 C (102.8 F) and a decrease in his appetite. On September 29, he began dragging his left leg and was unable to use it 1 day later.

The child received DPT/oral polio vaccine (OPV) at 2, 4, and 6 months of age. He was never breast-fed, had not traveled outside Mississippi, and had no known contact with anyone who had. He began attending a day-care center at the beginning of September 1987. Thirteen of the other 97 attendees had OPV between August 1 and

September 22, 1987.

The child was awake and alert and had right-sided otitis and possible ton-sillitis when he was admitted to the medical center. The neurological examination was normal, except that the muscles in the left hip and thigh were not functioning, and the muscles below the left knee were weakened. The left knee-jerk reflex was absent; the left ankle-jerk reflex was present but slightly weaker than the right. The plantar reflex was downgoing and equal bilaterally.

Lumbosacral X-ray films, magnetic resonance imaging of the lumbosacral spine, quantitative immunoglobulins, and skin tests for cellular immunity were normal. A lumbar puncture revealed normal glucose and protein and nine white blood cells (98% lymphocytes) in the cerebrospinal fluid. Nerve conduction studies and electromyograms of the lower left leg were normal except for absent or decreased activation of tested muscles.

A follow-up examination 4 months later showed a partial return of function in the lower left leg. The child was able to walk with a slight limp. Reflexes were present, but they were slightly weaker in the left leg than in the right. There was some atrophy in the left calf. These and other clinical findings were indicative of a lower motor neuron process, such as paralytic poliomyelitis, in the lower left leg

Stool specimens obtained on October 5, 6, and 8 all grew enterovirus 71 (EV71). Cerebrospinal fluid was not cultured for virus. Sera obtained on October 3, 4, 6, and 29 (7, 8, 10, and 33 days after onset of illness) all showed low but constant titers to the three serotypes of poliovirus (range 1:40 to 1:120), as would be expected for a child who had received three OPV vaccinations. The titers to EV71 were 1:720, 1:1,280, and 1:720 for the first, third, and fourth serum specimens, respectively.

Reported by: RR Hanson, MD, Univ Medical Center; H Myers, MD, Voice of Calvary Family Health Center, Jackson; FE Thompson, MD, State Epidemiologist, Mississippi State Dept of Health, Div of Field Svcs, Epidemiology Program Office; Div of Viral Diseases, Center for Infectious Diseases, CDC.

CDC Editorial Note: While flaccid paralysis is most often associated with poliovirus infection, several nonpolio enteroviruses, including EV71, have also been associated with paralytic disease. The etiology of this case is likely to be EV71 infection for three reasons. First, the serologic results were consistent with those expected for an 18-month-old child who had received three doses of OPV and had developed an antibody response to all three serotypes. Second, EV71 was the only virus isolated from the specimens under conditions in which poliovirus, if present, would have been isolated. Third, the antibody titers to EV71 were very high, as would be expected with a recent infection.

EV71 is unique among the nonpolio enteroviruses in its ability to occasionally cause outbreaks of severe central nervous system (CNS) disease including encephalitis and polio-like paralysis.1 EV71 was first described in 1974 from cases of CNS disease, including fatal encephalitis, occurring in California from 1969 to 1973.2 To date, the virus has principally been associated with outbreaks of hand, foot, and mouth disease (HFMD), upper respiratory symptoms, meningitis, encephalitis, and flaccid paralysis very similar to that associated with poliovirus infection.²⁻⁸ The clinical symptoms associated with any particular outbreak have varied widely. In California prior to 1973, in Australia in 1972,3 and in Sweden in 1973,4 meningitis was the predominant severe illness associated with outbreaks of EV71. In Japan in 1973 and 1978, 5,6 HFMD was the predominant syndrome, although CNS infections were frequently observed. In Bulgaria in 1975, 21% of about 700 patients with laboratory-confirmed EV71 infection developed paralysis, and 44 patients died. Fatal encephalitis occurred among patients in an outbreak of EV71 infection in Hungary in 1978.8 In the United States, a cluster of 12 laboratory-confirmed cases in the Rochester, New York, area in 1977 included two cases of transient poliolike paralysis.9 While isolates of EV71 have been identified sporadically in the United States, extensive spread of the virus has not been observed.

The enterovirus surveillance system at CDC received 49 reports of EV71 isolates from 1977 through 1987. Fifteen of these occurred in 1977; 11, in 1979; and 8, in 1987. No other year had more than four reported isolates. However, in the last 6 months, the Enterovirus Laboratory at CDC has received and characterized ten additional EV71 isolates including four from Alaska, two from Oklahoma, and four from Pennsylvania, bringing the total for 1987 to 18. Surveillance data on EV71 is probably not a sensitive measure of its presence because of the inability of most diagnostic virology laboratories to isolate or characterize

EV71 infection can be diagnosed by isolation or serologic studies. A variety of human and primate cell lines, including primary rhesus monkey kidney cells, diploid human lung fibroblast cells, rhabdomyosarcoma cells, and Vero cells, can be used to isolate

EV71. Growth of this virus is often slow compared to other enteroviruses. and multiple blind passages are often required to isolate it. Once isolated, the virus can readily be adapted to a wide variety of human and primate cells. Identification of an isolate is complicated by the absence of antisera to EV71 in the common enterovirus typing pools and by the limited availability of type-specific antisera.

Clinicians are encouraged to report suspected cases of paralytic illness due to enteroviruses to their local and state or territorial health departments. Enterovirus isolates from these cases can be sent through the local and state or territorial laboratories to the Division of Viral Diseases, Center for Infectious Diseases, CDC, for typing.

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Henoch-Schönlein Purpura—Connecticut

Mar 4, 1988 (Vol. 37, No. 8)—BE-TWEEN AUGUST 13 and December 15, 1987, a cluster of 20 cases of Henoch-Schonlein Purpura (HSP) involving children under 10 years of age was identified in Connecticut. In contrast, eight cases had been identified in the state during the first 7 months of the year. HSP is a vasculitis that involves the skin and other organ systems and primarily affects children.

The cluster was initially noted by a Hartford pediatric nephrologist who was consulted regarding eight children, four of whom became ill over a

2-week period.

Ten cases were identified in Hartford County, where case finding was the most intensive. Six of the ten patients lived in the city of Hartford and had onset of symptoms between October 15 and November 25 (attack rate for the city of Hartford, 2.9/10,000 children under 10 years of age). The other four lived in surrounding towns (0.5/10,000 children). Hispanic children accounted for five cases in Hartford County and had an attack rate more than five times that of either black or white children (Hispanic chil-4.0/10,000; black children, 0.8/10,000; white children, 0.5/10,000). The ten cases outside of Hartford County involved eight white and two Asian children. No confirmed cases were found in Bridgeport, a city with a demographic composition similar to Hartford's.

All 20 children had a rash character-

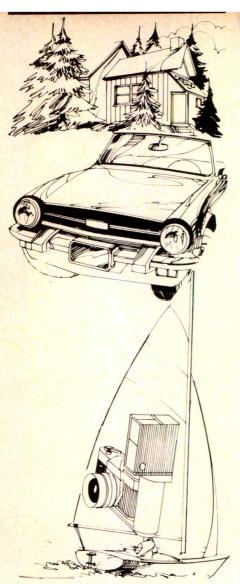
istic of HSP. Sixteen children developed arthritis, 16 had abdominal pain, and at least five had microscopic hematuria. Ten children were hospitalized. None died or developed serious complications.

CDC Editorial Note: HSP is identified by a characteristic rash most prominent on the buttocks and legs and is often associated with arthritis of the knee or ankle, abdominal cramping, or hematuria (1). As in this outbreak, the prognosis for the disease is generally good. However, a small percentage of children develop chronic glomerulonephritis.1,2 The number of children in the United States with renal failure resulting from HSP is unknown; however, it has been estimated that HSP is the cause of renal failure for 15% of the children on dialysis in Europe.3

Series of cases in the literature indicate seasonal changes in the incidence; the largest number of cases usually occur in the winter.24 An extensive search of the literature did not reveal any previous reports of clusters of HSP or of a predilection for Hispanic or urban children. The etiology of HSP is unknown; however, it is believed to be caused by an immunologic response to a variety of different stimuli.⁵ In individual cases, it has been linked to foods,6 medicines,7 toxins, insect bites, and various infectious agents. Approximately two-thirds of the children in three large clusters of HSP reported symptoms of an upper respiratory infection during the month before onset. 1,2,4 However, no agent was implicated as a cause of the symptoms.

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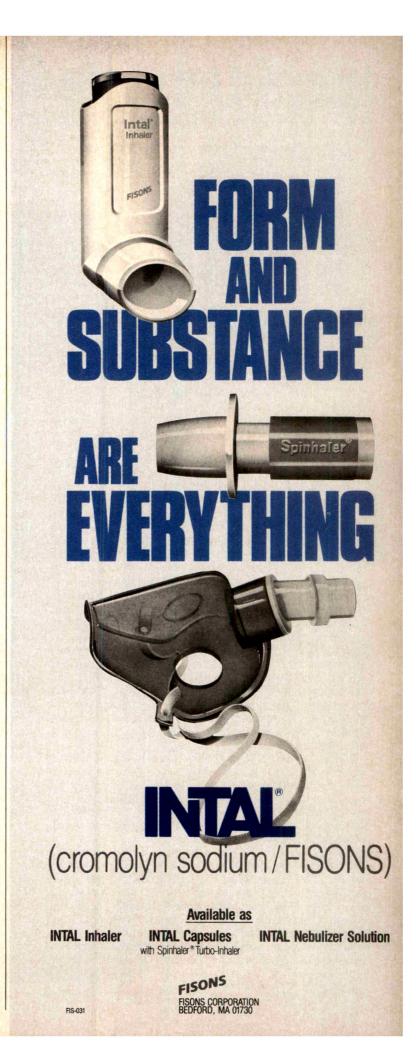
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The Editorial Board Speaks . . .

Laurence Finberg, MD





We detailed "Larry's" educational and career background at the time of his previous contribution to this section (AJDC 1986;140:201). Since that time he has been elected to the presidency of the American Board of Pediatrics, remains as chairman of the Committee on Nutrition of the Academy of Pediatrics, and holds the chair of the Department of Pediatrics, State University of New York Health Science Center at Brooklyn.

Larry's interests are broad, both in the medical world and elsewhere. He has been involved in setting policy for the nation in a variety of pediatric areas, including nutrition, certification and recertification, medical student and pediatric education, testing, national formulary and pharmacopeia, environmental hazards, graduate medical education, and editorial policies for scientific journals.

He is one of our most "critical" reviewers, in the best sense of that word. He cuts through to the core of a given report, noting and critiquing both the best and the worst. He is timely and always gives sound advice to the editor.

RESTRAINTS ON PUBLICATIONS

PHYSICIANS AND JOURNALS

It is seldom that one is given a public platform with an invitation to write about anything that is on one's mind. I shall take advantage of the opportunity here to reflect upon the modern relationship of the general press to the scientific and, more specifically, the medical literature. The marvelous technological advances of our time in the communications field have altered the old relationship in a number of ways. I wish here to address two of these alterations: the timing of the release of newly printed medical articles to the general public via the printed or electronic press and the posture of the medical journal and its editors in relation to the press.

Scientific progress, and I include clinical medicine here, moves slowly through the gathering, sifting, and analyzing of data, and through the opportunity for debate and conflicting opinions among peers. We expect that truth, or an approximation thereof for our time, will emerge. In general the process works. Sometimes it takes years and occasionally much longer. Also occasionally, the beauty or accuracy of a study is so obvious that it is instantly and correctly adopted. We have always held that it takes a trained mind to distinguish among these differing kinds of information. The danger is that untrained persons influenced by investigators who are self-serving will accept a harmful conclusion at face value.

The issue at hand is this: At what point should publication intended for professional peers be opened to the public? Clearly, an investigator has freedom to announce anything in any way at any time he or she chooses, including to the press. Why should one wish to accelerate the process in this way rather than await publication in the professional literature? The motive could be altruistic, eg, to save lives or prevent morbidity. It could also be to improve personal visibility and to help advance a career. While the latter motive is not necessarily evil, experience teaches that more harm comes from premature disclosure than from slow career progress; good work ultimately does get rewarded, and more solidly after restraint than after a flashy presentation. At least sometimes quick fame later becomes an embarrassment. Are there exceptions that call for the quick announcement of findings? If botulinus toxin

has been discovered in the water supply, we should all recognize the event as an exception and use more than the channels of scientific publication alone.

If the investigator chooses to go the route of publication in a peer-reviewed journal, however, should there be restrictions on release of the information prior to publication? Such journals (AJDC is one) confer a higher level of authenticity than a public relations release or a leaked story to a reporter. The PNEJM (the P is for prestigious, a word not included on the masthead but almost always accompanying citation of this publication in, for example, the New York Times) has a policy, widely publicized, that states that upon submitting an article for publication the author agrees that it has never been presented elsewhere (other than a scientific meeting) and data will not be released to the press until the day of publication. The journal itself embargoes publication of its (by now printed) material until the night before the official day of publication. The press generally honors the embargo, but recently (January 1988) there was a premature release that presumably came through a "leak" from an industrial source that had a financial stake in the article. That action resulted in editorial criticism of the policy rather than the leak.

Another action of many journals is to issue to journalists printed press releases of the journal's contents with abstracted articles frequently written by public relations staff, ostensibly to educate the journalists. Such releases sometimes appear weeks before the official publication date, followed by telephone calls to "experts" for comment.

I believe that the first of these policies is a good one in that it allows wide peer review to occur simultaneously with release of the article to the public. It is not censorship, since the author could have submitted his or her material elsewhere. I disagree with the second practice of initiating press releases. What is proposed as education for journalists is, I believe, self-serving for the journal that does it so that it can acquire that "P" or at least attract more attention, more subscribers, and more advertisers. If the investigator should exhibit restraint and encourage peer exchange before final acceptance by the medical community, then so should the journals. A little calm helps foster reason and helps smooth the process; what is good for the author's scientific reputation is also good for the publication's reputation. Good reputations for both enhance the credibility of our professional community.

Determinants of Pediatric Injuries

Sarah McCue Horwitz, PhD; Hal Morgenstern, PhD; Loretta DiPietro, MPH; Carol L. Morrison, MD

· Injuries are an important health issue for children. Previous research, however, has presented confusing and conflicting results on the determinants of childhood injuries, particularly psychosocial predictors, largely due to methodologic problems. The purpose of this analysis, based on a prospective follow-up study of 532 children, was to identify factors related to injuries encountered in a prepaid group practice during a 12-month period. Using logistic regression, we found four factors independently associated with the risk of at least one treated injury: high activity level, high rate of pediatric utilization for non-injury-related visits during the follow-up period, occurrence of a treated injury during the year preceding the follow-up period, and negative attitude toward medical care providers by the child's mother. In addition, four factors were found to be independent predictors of injuries judged severe enough to always warrant medical care: occurrence of a treated injury in the preceding year, high rate of pediatric utilization for noninjury-related visits during the follow-up period, working more than 15 hours a week outside the home by the child's mother, and more life events reported by the mother for the year preceding the follow-up period. Since family stressors are related specifically to the risk of more severe injuries, which are unlikely to escape medical attention, we conclude that these factors probably are related to the occurrence of common injuries of early childhood and not exclusively to utilization behavior. We therefore suggest that children from families with these characteristics be targeted for injury prevention strategies.

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Injuries are an important health issue for children. Forty to fifty thousand children are permanently disabled, and more than 1 million children receive medical treatment for injuries each year.^{1,2}

The terms accident and injury are often used interchangeably. An "accident" implies a random, unpredictable event resulting from obscure and uncontrolled causal sequences. However, epidemiologic studies of injuries have shown that they are nonrandom and have identified factors that may increase an individual's risk of injury. These factors include a greater exposure to hazardous environments, a decreased ability to avoid hazards, and a decreased resistance to injury.³

Research on injuries has generally been concentrated in three areas: (1) examination of the environment in which an injury occurred, (2) delineation of the agent involved in the injury, and (3) elucidation of the victim's behavioral characteristics and social situations. High injury rates in young children reflect a developmental susceptibility to injury. However, for certain subgroups of children who appear to be at particularly high risk for injuries (ie, the "injury repeater" and the "poison ingestors"), researchers have attempted to identify determinants other than developmental immaturity to explain the increased risk. This research has primarily examined child and family sociodemographic, behavioral, and psychosocial characteristics as predictors of injuries. The underlying assumption is that any of these factors can alter a child's exposure to hazards or decrease a child's ability to avoid hazards.

A number of studies have documented associations between family life events, such as serious family illness, frequent family moves unemployment or frequent job changes of the father, and the loss of a parent due

to divorce or separation,4-10 and childhood injuries. In addition to acute family life events, the relationship of chronic stressors and injuries has been examined. These stressors include maternal psychological disorder (eg, anxiety and depression), maternal physical illness, chronic unemployment, crowded housing, and low socioeconomic status (SES). The results from studies of chronic stressors have been less consistent than those of acute stressors. For example, parental occupational status was a significant predictor in some studies, 8,10,11 but SES and crowded housing were not related to childhood injuries in another.9 On the other hand, instances of maternal depression, illness, or psychosis consistently predicted higher rates of childhood injury. 4,6,10,12-14

The effect of family size and composition also has provided inconsistent results. Wadsworth et al⁷ found that children in stepfamilies and one-parent families had higher injury rates and hospital admissions during a five-year period than children with two parents. However, Taylor et al⁸ found that family type was not associated with childhood injuries but that young maternal age was. Studies of family size have usually found that large family size is associated with injuries in children. ^{6,8,12,15,16}

Several studies have evaluated the child directly to ascertain specific behavioral characteristics associated with injury. While there is often agreement as to how these children behave, there is disagreement as to why they behave as they do. Children who demonstrate higher rates of injury are typically described as impulsive, hyperactive, anxious, aggressive, rough, and less attentive. 26,7,9,12,15-18

Mathany et al¹⁹ attempted to isolate behavioral characteristics from environmental determinants of injury using twins. His results indicated that the twins who had more injuries at home were judged to be more active, more temperamental, and less attentive then their cotwins.

Risk-taking behavior is a characteristic often associated with higher injury rates in children. 5.16 However, the concept is quite vague and hard to quantify, since no valid index exists independent of injury behavior. Most assessments of risk-taking behavior rely on maternal subjective observation, often after injuries occur.

Langley et al²⁰ studied the relationship of 90 variables to childhood injuries and found no consistent differences between children with no injuries, one injury, and two injuries a year during a five-year period. A possible explanation for these findings may be that this study differed methodologically from others. Langley et al²⁰ utilized a longitudinal design to study children during their first five years of life. They also employed psychometric and standardized tests as well as mothers' reports.

In addition to child behavioral characteristics, several studies have demonstrated that history of injury is a risk factor for subsequent injuries. 6,9,12,21 However, like the studies of behavioral characteristics, many do not control for other factors that affect injury rates.

Much of what is known from studies about childhood injuries is distorted by a number of methodologic factors. First, several studies lack both reliable and valid measures for assessing the constructs of interest, especially maternal depression, acute stressors, and risk-taking behavior. While many studies claim to use life events indexes, acute stressors are often mixed with long-term or chronic stressors. This fusion of acute and chronic stressors, plus the lack of reliability and validity of these measures, lead to a lack of comparability between studies.

A second methodologic problem is that many studies ignore important predictors (eg, parental utilization behavior) and do not assess the possible interactions between predictors. For example, little attention has been paid to the possible modifying effects of sociodemographic characteristics on family stressors. It may be that con-

flicting results can be explained by the nonuniform effect certain life events have on childhood injury over different categories of other factors, such as SES.

A third problem is small sample sizes, causing lack of precision in the estimates. A fourth problem involves the types of injuries studied. Many studies involve only relatively severe injuries and, thus, the results may not be applicable to the majority of childhood injuries.

A fifth methodologic problem, particularly in studies assessing child behavior or personality characteristics, is that the assessment of the behavior is often done after the injury occurs. It is therefore difficult to differentiate between cause and effect, ie, the occurrence of injuries may have influenced the study factor (behavior).²²

Another consequence of retrospective designs is that observations generally depend on maternal recall, ie, the mother is asked to remember circumstances or events preceding or involving the injury episode. If, in fact, an injury can affect the behavior of a child, then it can certainly affect the mother's perception of the injury episode or assessment of her child's actions, thereby introducing strong bias into the estimation of effect.

Previous research on childhood injuries has presented confusing and often conflicting results on predictors, particularly on psychosocial determinants of injuries. We believe that these conflicting results may be due partly to the methodologic problems in previous work. Based on a prospective longitudinal design, we sought to identify factors related to the occurrence of any childhood injury encountered in a prepaid group practice during a 12-month period and factors related to injuries judged severe enough to always warrant medical care.

PATIENTS AND METHODS

The data in this report come from the Yale Pediatric Study, a follow-up investigation of more than 500 children who belonged to a prepaid group practice affiliated with Yale University, New Haven, Conn. This practice is open to faculty, students, and staff of Yale University. It offers comprehensive pediatric care without copayment and is affiliated with a major univer-

sity teaching hospital.23

The source population consisted of all families belonging to the prepaid group practice on Sept 1, 1981, and having at least one child under the age of 5 years on Dec 31, 1981. In 244 families in which more than one child was under 5 years of age, one child was randomly selected as the study subject. Of the 598 families who met these criteria, 65 (10.8%) refused to participate. Of the 533 interviewed mothers, one withdrew immediately after the initial interview, and 19 were identified during the baseline interview as not using the prepaid group practice as the regular source of care for their children. These 20 children were excluded from the analyses reported herein, leaving a sample size of 513 chil-

A baseline 45-minute structured interview with mothers was conducted by one of three specially trained research assistants who were blind to the study hypotheses. Following the interview, the children's medical records were abstracted to obtain information on birth history, developmental problems, major acute illnesses, chronic conditions, and utilization of the group practice for the year preceding entry into the study. Information from the medical records was used to develop a baseline health status measure for study children. During the 12-month follow-up period, information was collected on all visits to the prepaid group practice for participating children. For visits to the department of pediatrics, utilization data were collected through short questionnaires administered to parents and through encounter forms completed by clinicians during each appointment. For care in departments other than pediatrics and for after-hours care, utilization data were obtained from department visit logs and children's medical records.

Mothers' Baseline Interviews

For the purpose of these analyses, four categories of factors were considered: so-ciodemographic variables, health attitudes and beliefs, psychological distress and so-cial strain variables, and social network variables.

Sociodemographic Characteristics.—Included in these analyses are race, mother's age, education of the mother and her partner, current marital status, number of persons in the household, number of children in the family, current employment status of the mother and her partner, income, Duncan's index of SES,²⁴ child care arrangements, and satisfaction with child care arrangements.

Health Attitudes and Beliefs. - Percep-

Table 1.—Selected Sociodemographic Characteristics (Continuous) of Study Families and Children*

| | Observed Range | Mean | SD | |
|--|-------------------|------|------|--|
| Maternal age, y | 17-42 | 31.0 | 4.0 | |
| Maternal education, y | 4-19 | 16.0 | 2.3 | |
| Partner's education, y | 10-19 | 17.5 | 2.2 | |
| Socioeconomic score† | 7-96 | 75.0 | 20.0 | |
| Child's age, mo | 2-56 | 25.8 | 15.0 | |
| No. of household members | 2-11 | 3.8 | 1.1 | |
| No. of children in family | 1-9 | 1.7 | 1.0 | |
| Child's birth order | 1-9 | 1.6 | 0.9 | |
| No. of hours mother is employed weekly | 0-75 | 15.8 | 18.1 | |

*Data were obtained from all 513 study families for all variables except maternal education (512 [99%]), partner's education (500 [97.5%]; 13 families had no adult male members), and socioeconomic score (445 [87%]).

†Socioeconomic status could not be calculated for student families in which one partner was a student and the other partner was not working.

tion of a mother's health status and a mother's perception of her child's health status were measured using questions developed for the Rand Health Insurance Study.^{25,26}

The remaining health attitude and belief factors were taken from investigations by Mechanic²⁷ and Tessler and Mechanic.²⁸ These included propensity to seek care, experience with common childhood illnesses, attitudes toward medical providers, satisfaction with pediatric care, and health locus of control.

Psychological Distress and Social Stressor Factors.—Our measure of psychological distress was the Center for Epidemiologic Studies Depression Scale.²⁰ The measure of acute (number of events in the past 12 months) life stressors was adapted from the Recent Life Changes Questionnaire,³⁰ and chronic life strains were measured by items developed and reported by Pearlin and Schooler³¹ and Ilfeld.²²

Social Network Measures.—Following the general framework outlined by Mitchell²³ and other sociologists interested in network analysis, ³⁴⁻³⁶ measures were developed for structural characteristics of the mother's social network, including size, density, intimacy, durability, multidimensionality, reciprocity, geographic proximity, frequency, and homogeneity.

The second network dimension we investigated was the subjective appraisal of network support (ie, social support). Each mother was asked how supported she felt in the last few months when she needed help with household tasks, emotional support, and financial aid, and who, if anyone, provided this support.

The third network dimension evaluated was the mother's tendency to call on network members for assistance.²⁴ These

items differed from the support questions in that they asked which individuals the study mother *would* approach rather than who, in the last few months, *did* provide assistance or support.³⁷

Child Information

Charts were abstracted for sociodemographic information, allergic conditions, chronic medical problems, major acute illnesses, speech and language problems, neonatal complications, early growth abnormalities, and utilization of the group practice during the 12-month period preceding enrollment in the study.

We did not want to rely solely on the mothers' assessments of their children's health status, so we developed a measure of health status from information contained in the medical record (ie, information available before the follow-up period). All conditions or diseases found in the children's charts were ranked 1, minor; 2, moderate; or 3, major. If a child had more than one disease or condition, only the score of the most severe condition was used. If a child had no diseases or conditions, a score of 0 was given.

Since our identification of childhood injuries was based on the use of medical services, it is important to control for utilization patterns when testing effects on this outcome measure. We controlled for utilization in two ways. First, when analyzing all injury-related episodes, we adjusted for the child's annual utilization rate for non-injury-related visits during the study period. Second, we used two outcome measures, one of which is not likely to be altered by differences in utilization behavior.

Outcome Variables

Total injury episodes were derived by summing the number of first visits for

Table 2.—Selected
Sociodemographic Characteristics
(Categorical) of Study Families and
Children

| Variable | No. | (%) |
|------------------------------------|-----|--------------|
| Maternal race | | |
| White | 415 | (81) |
| Nonwhite | 98 | (19) |
| Marital status | | |
| Married | | (96) |
| Unmarried | 21 | (4) |
| Family income* | | |
| <\$8999 \$0000 \$17,000 | | (11) |
| \$9000-\$17999 \$18000-\$26999 | | (25) (28) |
| \$18000-\$26999 \$27000-\$35999 | | (16) |
| >\$36 000 | | (18) |
| Father's employment | | \ <u>'</u> |
| status† | | |
| Employed | 394 | (79) |
| Student | | (20) |
| Other | | (1) |
| Mother's employment | | |
| status | | Farmen. |
| Employed | | (52) |
| Student | 47 | |
| Housewife Other | | (36) |
| Otner Child's sex | 10 | (3) |
| Critics sex | 259 | (50) |
| F | | (50) |
| Child's disease | | |
| score | | |
| No conditions | 294 | (57) |
| Minor condition | 102 | (20) |
| Moderate/major condition | 117 | (22) |

*Nine missing values.

Table 3.—Types of Medically Attended Injuries

| injury | Total No. | No. Classified as Severe Enough to Warrant Medical Attention | | |
|--------------------------|--------------|--|--|--|
| Contusions/ abrasions | 31 | 2 | | |
| Lacerations | 28 | 17 | | |
| Burns | 12 | 6 | | |
| Impacted objects | 4 | 1 | | |
| Fractures | 2 | 2 | | |
| Poison ingestions | 2 | 0 | | |
| Miscellaneous | 10 | 2 | | |
| Total | 89 | 30 | | |

separate injuries during the 12-month follow-up period. Since few children (4.3%) had more than one injury episode and since most children were followed up for ten to 12 months, injury episodes were categorized as present or absent.

[†]Thirteen families had no adult male member.

Table 4.—Crude (Bivariable)
Relationships Between Selected
Sociodemographic, Health Attitude
and Belief, Distress/Strain,
Social Network Features, and
an Injury Episode (N=513)

Variable

| Variable | P |
|--|--------------------------|
| Sociodemographic | |
| Child's age | .617* |
| Child's birth order | .551* |
| Child's sex | .157† |
| Child's baseline | |
| health score | .512† |
| Child's activity | |
| level, high | .009† |
| Child's history of past | 0014 |
| injuries, present Child's current utilization | .001† |
| pattern, high | .005† |
| Mother's age | .947* |
| Mother's education | .429* |
| Partner's education | .909* |
| Current marital status | .120† |
| Maternal race, white | .075† |
| Socioeconomic score | .0751 |
| (family) | .184* |
| Ethnicity | .736† |
| Income (family) | .853† |
| Household size | .982* |
| No. of children | |
| in family | .977* |
| Use of child care | .298† |
| Type of child care | · |
| (multiple-provider vs | |
| single-provider centers) | .379† |
| Satisfaction with | |
| child care | .587* |
| No. of hours | |
| mother works (≤15, >15) | .116* |
| Mother's Health Attitudes | |
| and Bellefs | |
| Mother's perception of her health | 000* |
| KARA U MARA 185 MINI | .233* |
| Mother's perception of child's health | .598* |
| Health locus of control | .343* |
| Attitudes toward | .040 |
| medical providers, negative | .031* |
| Satisfaction with | |
| pediatric care, more satisfied | .073* |
| Familiarity with | |
| common childhood illnesses | .154* |
| Mother's Distress/Strain | |
| Center for Epidemiologic Studies | e - And The State (1988) |
| Depression Scale | .785* |
| Life events | .254* |
| Financial strain | .291* |
| Marital strain | .264* |
| Homemaking strain | .624* |
| Occupational strain | .816* |
| Role conflict strain | .925* |
| Social Network | |
| Size | .866* |
| Density | .969* |
| Multidimensionality | .557* |
| Dispersion | .489* |
| Feelings of support | .662* |
| Tendency to call on | |
| network members | .171* |
| | |

^{*}Unpaired t test for continuous predictors

†x² test for categorical predictors.

Since the use of medical care for pediatric injuries (our outcome variable) is probably influenced by the tendency of parents to seek care and by the injury occurrence itself, we created another outcome measure that we felt was less influenced by such utilization behavior. Looking at the medical injuries encountered in the prepaid practice, three of the authors (S.M.H., L.D., C.L.M.) independently rated the severity of the injury on a binary scale. An injury was judged to be severe if it always warranted medical attention. For example, a simple head contusion, without loss of consciousness, dizziness, or nausea, was scored as nonsevere. However, a contusion with any one of these symptoms was rated as severe, indicating the need for medical care. Additionally, injuries were scored using the Abbreviated Injury Scale criteria.38 There was perfect agreement among the three authors' assessments and the Abbreviated Injury Scale scoring. Due to the minor nature of most injury episodes, those demanding medical attention were clear-cut. Again, a dichotomous outcome measure was created. Of the 89 children who sustained an injury, 30 (37%) received an injury judged severe enough to always warrant medical attention.

Analytic Methods

The crude (bivariable) analyses and logistic modeling were done using the Statistical Analysis System (SAS) computer program package. Crude analyses used χ^2 tests for categorical predictors and unpaired t tests for continuous predictors. For logistic modeling, predictor variables were entered into the model by type of variable-first, sociodemographic variables, then health attitudes and beliefs, followed by psychological distress/social stressor variables, and, finally, social network variables. Model building was initiated using the variables correlated with an injury episode and severe injury in the crude analyses, but all independent variables were considered during the process. Once the "best" main effects model had been built, the following interactions were tested: those between all main effects in the model, those between variables related to injury episodes in the crude bivariable analyses but not retained in the model and main effects in the model, and those interactions suggested by previous research (eg, between sociodemographic factors, such as SES and income, and life events).

RESULTS

The study population is described in Tables 1 and 2. At the initial interview, women, on average, were 31 years old,

primarily white (81%), usually married (96%), and often employed (52%). Working mothers averaged 16 hours a week on the job, with 24.5% spending 36 or more hours a week on the job. The study mothers and their spouses were well educated. Study mothers had an average of 16 years of education (ie, a college degree), and their spouses or partners had completed an average of 17.5 years of education. The study children ranged in age from 2 to 56 months, with a mean age of 26 months at the time of the study enrollment. These children lived in nuclear families (3.8 people in the household), were most often first born (59.5%), and were healthy. Four (<1%)of the children had been diagnosed as overactive or aggressive by their medical care provider. Four hundred twenty-four children (82.6%) had no injury episodes in the follow-up period, 67 (13.1%) had one injury episode, and 22 (4.3%) had two or more injury-related episodes. The types of injuries sustained by children and the number judged severe enough to always warrant medical attention are shown in Table 3.

Table 4 shows the crude (bivariable) relationships between the predictor variables of interest and any injury episode. Strong positive relationships are seen between an injury episode and three child-related variables: activity level, use of medical care for an injury within the preceding year, and the utilization rate for non-injury-related visits during the follow-up period. Children who were noted to be active, who had a medical record entry for at least one previous injury, and who were high utilizers in the followup period had a higher risk of treated injuries.

Three maternal variables showed a crude relationship to an injury episode. Maternal race (specifically being white) and maternal health attitude and belief measures—general attitude toward medical providers and satisfaction with their children's pediatric care—were related to having an injury episode. Women who had negative attitudes toward the medical establishment as a whole but were satisfied with the pediatric care provided by the prepaid practice were more likely

o have children with an injury epiode.

The final multivariable model reults are shown in Table 5. Of the six ignificantly associated variables from he crude analyses, four remained sigificant independent predictors of inury episodes (P<.05). Children who and a high activity level, a history of ise of medical services for injuries, ind a high rate of medical care utiliation in the follow-up period, as well is those whose mothers had negative ittitudes toward the medical estabishment, had a higher risk of treated njuries. The two variables associated wth injury episodes in the crude analrsis-race and satisfaction with their shild's pediatric care—did not remain n the model, most likely due to their association with utilization. None of the other sociodemographic, health attitude or belief, distress/strain, or social network factors were significant predictors of injury episodes as main effects or interactions once the effects of these four factors were accounted for

The crude associations between the predictor variables and occurrence of an injury episode judged severe enough to warrant medical attention are shown in Table 6. The same child variables were associated with any injury episode requiring medical attention: high activity level, previous use of medical services for an injury, and high use of services in the followup period. However, the maternal variables associated with an injury episode judged severe enough to require medical attention are quite different. If a mother worked more than 15 hours a week, had a negative perception of her own health, was very familiar with common childhood illnesses, and reported many stressful life events, her child was more likely to have had an injury episode requiring medical attention in the follow-up period.

The logistic regression results for episodes requiring medical attention are shown in Table 7. Hyperactivity was excluded from the final model due to problems associated with its low frequency (1%). When added to the model shown in Table 7, however, the estimates for the other predictors do not change. In this population, the

Table 5.—Estimated Logistic Regression Coefficients for the Final Model Predicting an Injury Episode (N = 513)

| Predictor* | β SE | | P | Odds Ratio | 95% Confidence Interval (Odds Ratio) | |
|-------------------------------------|-------------|-------|-------|---------------|---|--|
| Intercept | 2.493 | 0.248 | | | 1.7 | |
| High concurrent utilization | 0.799 | 0.255 | .002 | 2.22 | 1.35-3.66 | |
| High activity level† | 2.561 | 1.184 | .031 | 12.95 | 1.27-131.85 | |
| Negative attitudes toward providers | 0.511 | 0.247 | .039 | 1.67 | 1.03-2.71 | |
| History of previous injury | 0.922 | 0.265 | <.001 | 2.51 | 1.50-4.27 | |

*All binary coded 0,1; odds ratio = Exponent[β]

†This variable has limited dispersion (only four children were diagnosed as hyperactive) and may be a bad candidate for the model.

model developed for injuries requiring medical attention presents a different picture than the model developed for total injury episodes. Children with a past episode of medically attended injury, those who had a high utilization rate in the follow-up period for noninjury-related visits, those whose mothers worked more than 15 hours a week, and those whose mothers reported a large number of stressful life events were more likely to have an injury episode requiring medical attention in the follow-up period than were children without these personal and family characteristics. Again, once the effects of these four variables were accounted for, there were no other significant main or interaction effects.

We were particularly interested in the relationships of life events and number of hours of maternal employment to the risk of an injury requiring medical attention. Consequently, we sought explanations for these relationships. Based on the work of Beautrais et al,4 Brown and Davidson,10 and Sibert and Newcombe,6 we hypothesized that both relationships with injury episodes requiring medical attention were due to strain experienced by the mother. We looked at a number of strain variables-marital, financial, occupational, and role-and our depression score to determine whether any of them could account for the relationships. None of these factors could explain either the relationship between number of hours worked or life events and these more severe injuries. We then assessed the relationship of child care to injuries requiring medical attention. Neither type of child care (ie, large multiple-provider centers vs single-provider situations) nor satisfaction with child care arrangements explained these relationships. Because we had no information about the circumstances surrounding these injuries, further exploration of explanations was not possible.

COMMENT

We looked first at determinants of any injury episode from the crude analyses and found six related factors. Child activity level, history of past injury, and race are often cited as injury predictors. Three factors that are usually related to utilization of services—two maternal health attitudes and current utilization pattern—were also related to total injury episodes. No psychosocial factors were related to total injury episodes in the bivariable analyses.

The multivariable results showed that high current utilization, high activity level, history of previous injury, and a negative attitude toward medical care providers were significantly related to injury episodes. Race, which was strongly related to medical care utilization, was not a predictor when utilization was controlled for. After the inclusion of utilization in the model, the estimated effect for race decreased. These results clearly point out the necessity of adjusting for family utilization patterns when using injury data collected from utilization records.

The predictors associated with injuries judged severe enough to warrant medical care present a different picture. Injury during the previous 12 months (13% with factor present vs 4% with factor absent) and high concurrent utilization (8% injured among high utilizers vs 3% among low utilizers) probably had an effect on the presence of injuries requiring medical

Table 6.—Crude (Bivariable)
Relationships Between Selected
Sociodemographic, Health Attitude
and Belief, Distress/Strain, Social
Network Features, and an Injury
Episode Severe Enough to Warrant
Medical Attention (N = 513)

| Vadable | |
|---|----------------|
| Variable Scaledamoveschi | Р . |
| Sociodemographi Child's age | c .598* |
| Child's birth order | .323* |
| Child's sex | .485† |
| Child's baseline | |
| health score Child's activity | .174† |
| level, high | .001† |
| Child's history of past | .0011 |
| injuries, present | .005† |
| Child's current utilization | , |
| pattern, high | .001† |
| Mother's age Mother's education | .911* |
| Partner's education | .081* .682* |
| Current marital status | .244† |
| Maternal race | |
| (white, other) | .191† |
| Socioeconomic score | 2004 |
| (family) Ethnicity | .853* 678± |
| Income (family) | .678† .566† |
| Household size | .437* |
| No. of children | |
| in family | .603* |
| Use of child care | .371† |
| Type of child care | |
| (multiple-provider vs single-provider centers) | .891† |
| Satisfaction with | .0011 |
| child care | .844* |
| No. of hours | |
| mother works, >15 | .032† |
| Mother's Health Attitudes as | nd Bellefs |
| Mother's perception of | |
| her health, lower perceived health | .046* |
| Mother's perception of | .040 |
| child's health | .741* |
| Health locus of control | .784* |
| Attitudes toward | 4054 |
| medical providers Satisfaction with | .195* |
| pediatric care | .539* |
| Familiarity with | .505 |
| common childhood illnesses, | |
| more familiarity | .064† |
| Mother's Distress/Str | ein |
| Center for Epidemiologic Studie | es |
| Depression Scale | .842* |
| Life events, | 0.40* |
| more life events Financial strain | .043* .826* |
| Marital strain | .776* |
| Homemaking strain | .366* |
| Occupational strain | .909* |
| Role conflict strain | .507* |
| Social Network | |
| Size | .714* |
| Density | .291* |
| Multidimensionality | .634* 922* |
| Dispersion Feelings of support | .923* .150* |
| Tendency to call on | . 100 |
| network members | .241* |
| State of the Control | |

^{*}Unpaired t test for continuous predictors. $\dagger \chi^2$ test for categorical predictors.

Table 7.—Estimated Logistic Regression Coefficients for the Final Model Predicting an Injury Episode Severe Enough to Warrant Medical Attention (N = 513)

| Predictor* | β | SE | P | Odds Ratio | 95% Confidence Interval (Odds Ratio) |
|-------------------------------|-------|-------|-------|---------------|--|
| Intercept | 4.887 | 0.556 | <.001 | | |
| Past Injury | 1.101 | 0.400 | .006 | 3.01 | 1.37-6.57 |
| Mother Works >15 Hours Weekly | 0.766 | 0.400 | .056 | 2.15 | 0.98-4.60 |
| Life events score† | 0.070 | 0.037 | .057 | 2.01 | 0.98-4.16 |
| High concurrent utilization | 0.996 | 0.450 | .027 | 2.71 | 1.12-6.54 |

^{*}All binary except life events score.

attention due to continuing environmental or behavioral influences. More intriguing were the effects of maternal employment hours and life events. If women worked more than 15 hours a week, their children were twice as likely to experience an injury requiring medical attention than if they worked less than 15 hours a week (8% vs 4%). We attempted to explain this finding with two sets of hypotheses. First, we hypothesized that working women with young children experience more role strain than nonworking women with young children. We looked at home-occupational strain, employment strain, marital strain, financial strain, parenting strain, and consistent day-care arrangements, and none of these variables explained the relationship.

The second hypothesis we tested concerned the role day care played in severe injury. We hypothesized that either day-care settings with higher staff-to-child ratios or those with which parents were dissatisfied might explain this relationship. Unfortunately, neither factor explained the association, and the lack of information concerning the environment in which the injury occurred prevented further analysis.

A dose-response trend was found between number of family life events and risk of injury severe enough to warrant medical attention. In the 40% of families with eight or fewer life events a year, 3% of the children had an injury severe enough to warrant medical attention; in the 40% of families with nine to 13 life events a year, 7% of the children had a severe injury; and in the 20% of families with 14 or more life events a year, 10% of children experienced an injury requiring med-

ical attention. We investigated whether particular types of events, such as deaths, moves, unemployment, and negative or uncontrollable events, were responsible. In our population, it was the total number of events rather than any particular type of event that was important. We next looked at whether maternal depression or any of the strain variables accounted for the relationship and again found no support for this explanation.

As with any research, there are limitations to our ability to generalize to other populations. Our study population was young, primarily white, and middle class; there was relatively little variability in educational level, family size, or marital status. Consequently, the absence of associations between many previously cited sociodemographic characteristics and injuries may be due to the homogeneity of our study population on these variables.

A second limitation of our study was the lack of information concerning the circumstances in which the injury took place. Because of the prepaid practice's policy of having injuries seen in their urgent visit area rather than the department of pediatrics, it was logistically impossible to interview families about children's injuries. Consequently, we had to rely on medical records and intake log information, which, while detailed concerning the injury itself, contained little information on the circumstances surrounding the injury. What information we did have led us to believe that children were not usually passive victims. Only one child sustained an injury while a passenger in a motor vehicle. Most descriptions of the injuries included some action on the child's part (eg, fell from a tree while playing). Similarly,

[†]Odds ratio corresponds to a difference of ten life events per year.

while having too little consistent data to draw conclusions, the descriptions we did have of the injury circumstances specifically for five of the six severe burns indicated that the injuries occurred in the child's home while in the care of parents rather than other caretakers.

A final limitation on generalizability was the nature of the injuries we considered severe enough to warrant medical attention. When using a standard scoring system such as the Abbreviated Injury Scale,³⁸ these injuries all received a score of 2 (moderate). No injury was ranked as severe, critical, or fatal. This concentration on less severe injuries did not allow conclusions to be drawn about the predictors of life-threatening injuries.

Even with these limitations, our results have implications for future injury research and pediatric practice. Our data show that different factors predict total injury episodes and in-

jury episodes severe enough to warrant medical attention. Specifically, health attitudes are important predictors of any injury episode, while maternal employment and life events are important predictors of more severe episodes. These results suggest that while certain health attitudes predict the use of medical care for childhood injuries, they do not predict the actual occurrence of these injuries. Consequently, not adjusting for utilizationrelated features may lead to incorrect conclusions concerning risk factors for childhood injuries. A clear example of this problem is that, in our data, the previously observed association between race and injury appears to be due to the tendency for white families be higher overall utilizers of children's health services. Further studies of injuries must control for family utilization patterns.

Our data have even more important implications for pediatric practice. Given the small return in behavioral

change for considerable efforts in patient education, it seems reasonable to target injury prevention efforts to groups of patients who appear to be at particularly high risk for injury. Our data suggest that children with a history of injuries, those who are high utilizers of medical care, those coming from families experiencing multiple stressors, and those with mothers who work more than 15 hours a week are more likely to experience an injury requiring medical attention. Whether this excess risk is due to inadequate parental supervision, a child's internalization of family stress expressed by "acting out" behavior, or a harried parent's inability to monitor out-ofhome care, it seems reasonable to target patients with these characteristics for intensive injury prevention strategies.

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Behavioral Research Toward Prevention of Childhood Injury

Report of a Workshop Sponsored by The National Institute of Child Health and Human Development, Sept 3-5, 1986

Peter C. Scheidt, MD, MPH (Chairman), and Workshop Participants

 At a recent workshop sponsored by the National Institute of Child Health and Human Development, Bethesda, Md, injury and child behavior researchers recommended continued expansion of both directed research on control of specific injuries and basic research on mechanisms that underlie many or all injuries. Prevention of injuries that are not amenable to environmental control will require change in human behavior. Important research questions to address this goal include the following: How do identified risk factors influence the occurrence of injuries? How do children learn behaviors that alter the rate of injury? How do child developmental factors contribute to safety and injury? Innovative methods are needed, such as measure of environmental hazards, exposure to risk, and precursors of serious injuries. These approaches expanded by a broadened base of investigators should help reduce childhood mortality and morbidity due to injuries.

(AJDC 1988;142:612-617)

Public health workers, child care providers, and many parents are painfully aware that injuries have emerged as the greatest risk to the life and health of children in the developed world. Unintentional injuries account for approximately 50% of all deaths of children aged 1 to 19 years, with motor vehicle—related deaths leading the list for each age

category (Table). The National Institute of Child Health and Human Development (NICHD), Bethesda, Md, whose mission is to stimulate, support, and conduct research to ensure the optimal development and welfare of children, has refocused its attention on this threat to the well-being of children.8 Institute staff recently held a workshop on approaches to behavioral research in prevention of childhood injury to stimulate interest in research on this problem, to identify key research issues, and to identify research methods needed for development. Workshop participants included a small working group of researchers and practitioners in the area of childhood injury control and behavioral scientists who have conducted research in this area. The aim of this report is to present some of the issues regarding behaviorally oriented research toward injury prevention in children and to serve as encouragement and guidance to potential investigators with regard to possible directions for research and specific methodological problems common to this field. First, conceptual issues are defined with regard to several major approaches or strategies employed in control of childhood injuries. Second, some methodological obstacles and problems faced by researchers concerned with childhood injuries are described. Finally, the report summarizes recommendations for researchable questions and methods to be developed.

GENERAL APPROACHES

Consideration of a research agenda for prevention of childhood injuries requires definition of major questions

to be asked and general approaches to be examined. In the following section. descriptive epidemiology, health education, behavioral analysis, and a developmental perspective are briefly examined with regard to their relative contributions and potential problems for control of childhood injury. This examination is undertaken with the understanding that, ultimately, injury prevention must entail at least some behavior changes by someone (eg, parents, children, legislators, judges, educators, manufacturers, physicians).4 Strategies to motivate these behavior changes are needed and require understanding and knowledge of the complex processes involved.

Descriptive Epidemiology

The study of childhood injuries has predominantly employed the classic epidemiological model, using agent, host, and environment^{9,10} to define factors that identify subpopulations at increased risk. This field of investigation has expanded greatly during the past decade. 8,11-17 Consequently, a picture of who is being injured is emerging with increasing clarity, defined by an expanding list of risk factors, such as poverty, family stress, maternal illness, substandard child care, recent environmental change, and increased activity. Application of this information can point to both opportunities and limitations for intervention. As a systematic tool to identify potential countermeasures, Haddon¹⁸ has offered a model for establishing priorities for intervention based on an analysis of energy transfer as an agent of injury. In this well-known model,19 ten basic strategies for establishing countermeasures to a given injury are listed in progressive order. The devel-

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A complete listing of participants in the NICHD Workshop appears at the end of this article.

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| Leading Causes of Injury-Related Deaths in Infants, Children, and Adolescents, 1984* | | | | |
|--|---------------|----------------|--|--|
| Age, y, and Cause of Death | No. of Deaths | Mortality Rate | | |
| <1 Motor vehicle | 161 | 4.42 | | |
| Inhalation of food or object | 153 | 4.20 | | |
| Fires, burns | 136 | 3.73 | | |
| Drowning | 70 | 1.92 | | |
| Falls | 28 | 0.77 | | |
| All unintentional injuries | 838 | 22.98 | | |
| Total deaths from all causes | 39 580 | 1085.57 | | |
| -4 Motor vehicle | 977 | 6.87 | | |
| Fires, burns | 606 | 4.26 | | |
| Drowning | 556 | 3.92 | | |
| Inhalation of food or object | 118 | 0.83 | | |
| Falls | 86 | 0.61 | | |
| "Accidental" poisoning | 77 | 0.54 | | |
| All unintentional injuries | 2814 | 19.80 | | |
| Total deaths from all causes | 7372 | 51.87 | | |
| 5-14 mg/s | | | | |
| Motor vehicle | 2263 | 6.66 | | |
| Drowning | 494 | 1.45 | | |
| Fires, burns | 466 | 1.37 | | |
| "Accidental" firearms | 253 | 0.74 | | |
| Falls | 68 | 0.20 | | |
| "Accidental" poisoning | 56 | 0.16 | | |
| All unintentional injuries | 4198 | 12.36 | | |
| Total deaths from all causes | 9076 | 26.71 | | |
| I5-19 Motor vehicle | 6495 | 34.58 | | |
| Drowning | 553 | 2.94 | | |
| "Accidental" firearms | 265 | 1.41 | | |
| "Accidental" poisoning | 184 | 0.98 | | |
| Fires, burns | 169 | 0.90 | | |
| Falls | 146 | 0.78 | | |
| All unintentional injuries | 8466 | 45.07 | | |
| Total deaths from all causes | 15213 | 80.93 | | |

*These 1984 statistics were obtained from the National Center of Health Statistics, Public Health Service, US Department of Health and Human Services.

†Deaths per 100 000 population in age category.

opment of such models provides an important framework for the application of epidemiological information to design interventions to reduce childhood injuries. However, it is becoming increasingly apparent that as the rates of mortality and disability from childhood injuries remain stubbornly high, despite expanding knowledge of who, when, and where children are injured, work must increasingly focus on understanding the causes and mechanisms that precipitate injuries, the hows and whys. Based on this understanding, interventions to interrupt this process must then be developed and evaluated.

Health Education

Programs of injury control have historically relied on health education as an important strategy for preventing childhood injuries.20-23 Use of the educational approach has been driven by the logic and assumptions that improvements in knowledge and attitudes induce behavior changes that in turn lead to reductions in childhood injuries. This strategy, accepted uncritically for many years, has more recently met with mixed and often disappointing results when subjected to careful evaluation.24-26 In general, as rigor of study design and use of target outcome measures (actual injury rates) have increased, the rates of reported successes have tended to decrease correspondingly.27 For example, a carefully designed controlled clinical trial of a provider-based health education program to reduce household injuries28 failed to demonstrate reduction of household hazards. Counseling to reduce poisoning, with the aid of "Mr Yuk"25 stickers for poisonous substances, failed to produce desired results in the high-risk toddler-aged children. The now-classic controlled advertising trial of community through cable television on the use of seat belts resulted in no difference in seat belt use for families exposed to the message campaign.25 These roports and others30-33 have raised doubts and dampened enthusiasm regarding the health education strategy in controlling childhood injury, 10,26,34

However, credible studies have also reported some limited positive outcomes from application of educational messages. Christophersen and Sullivan35 and others22,36-38 have demonstrated increased compliance with child restraint use in response to educational approaches. Miller et als9 showed that promoting the use of smoke detectors can be at least partially successful in inducing parents to obtain and install the devices. In sep-Fortenberry and studies, Brown⁴⁰ and Preusser and Blonberg⁴¹ demonstrated some reductions in pedestrian injuries for 6- and 7-year-old children by employing a variety of educational approaches focused on high-risk groups. Recent reports from New Zealand⁴² and Vermont⁴³ attest that positive outcomes from educational endeavors are more likely when multifaceted, community-wide programs are employed. Success is likewise enhanced when educational messages are coupled with legislative activity27,44 or other modalities of persuasion.

These few examples serve to point out that the issues regarding the educational strategy are complex and still not well understood. Evaluation of educational approaches must look beyond whether a single approach results in decreased associated events. The focus for research of the educational approach should address such issues as the identification of subpopulations who may respond differentially to educational intervention, the mechanisms of how some approaches appear to be effective and others do not, and how the high level of knowledge and/or performance³⁰ of some populations is achieved and might be spread to others.

Behavioral Analysis

A widely accepted view of the relative value of injury-control strategies holds that effectiveness in reducing injury is inversely proportional to the frequency of actions required by individuals—the "passive egy."1,4,10,25 However, for many hazards, the means do not currently exist to control environmental exposure, and different approaches using principles based on other aspects of human behavior are needed if we are to reduce exposure to hazards. The challenge remains for childhood injury researchers and behavioral scientists to develop effective and practical methods for accomplishing this goal.

A behavioral analysis of the injury process can help us to formulate approaches to answer this challenge. 45,46 This approach usually first asks whether a behavior can be altered by environmental conditions and then whether these conditions can be used to design an intervention based on learning principles. Experience with the "intensive care unit (ICU) syndrome" serves as an example of this approach.47 When in an ICU, some children appear markedly disengaged from their environment. This is similar to behavior that is experimentally produced by the use of aversive events in a controlled manner, termed conditioned suppression.48 Interventions, derived from the basic research on conditioned suppression, that add positive events to the ICU environment and make the aversive procedures more predictable have been able to modify the syndrome.49 In another example, pica and mouthing behaviors in children have been demonstrated to dramatically decrease through similarly based behavioral analysis and intervention.50-52 Such examples demonstrate that objective behavioral assessment can be coupled with applied learning theory to effect therapeutic and protective changes in behavior. Similar innovative approaches applied to injury-producing hazards faced by children when passive interventions are not possible could lead to the design of effective behavioral countermeasures.

Developmental Perspective

The developmental differences of children are major factors responsible for differences in vulnerability to various injuries. 5,58 An analysis of the developmental changes in interaction between parent and child reveals important insights into the possible mechanisms of childhood injury and possible interventions. For example, the first year of life, marked by bonding and close maternal-infant interaction, contains relatively little parent teaching compared with successive years.54 However, in the second year, dramatically increased demands for supervision accompany progressive gross motor development. The development of object permanence, ie, stable mental images of absent objects or people, introduces the new ability to seek hidden and potentially dangerous objects. 53 The third year brings a level of self-regulation that enables the child to remember, discriminate, and increasingly direct his or her own actions. During this latter phase, frequent limit violations lead to the need for nearly constant monitoring. 55 Although, at 3 to 4 years of age compliance increases markedly, out-of-sight compliance remains relatively poor, and the inability to generalize from concrete experiences limits learning and teaching of injury prevention. By 6 to 10 years of age, large gains in reasoning and delayed gratification are offset by an emerging sense of adventure and daring. At this age, the locus of control becomes one of coregulation between parent and child, but limitations of competencies are frequently underestimated by both parent and child. In adolescence, the development of formal operations in thought⁵⁶ is accompanied by feelings of uniqueness and even immortality. These developments, combined with the needs to assert independence, to experiment, and to imitate peers, can lead to serious consequences.

These examples of development and behavior control in relation to risks of injury illustrate the importance of child development and family relationships as factors in understanding the genesis, mechanisms, and control of childhood injury. Thus, the relationship of behavior to psychomotor and psychosocial development should be carefully considered when examining the process of childhood injury and is itself an important topic for research to improve our understanding and ability to control childhood injuries.

Summary of General Approaches

It is apparent that research in injury prevention involves multiple perspectives and requires interdisciplinary approaches. At one extreme, there appears to be a multiplicity of processes that independently lead to various injuries of children. Given this, we are consigned to multiple avenues of applied investigation, each limited in applicability to its own area. At the other extreme, there is the hypothesis of a unifying mechanism or model that underlies many or all injuries and that could be amenable to description and intervention-the "Northwest Passage" or "Holy Grail" of childhood injury. This latter theory would encourage a focus on basic research for mechanisms with wide generalizability. Although this dichotomy may be useful for argument and conceptualization, in reality simultaneous pursuit of both approaches is important. Directed epidemiological research can point to interventions for single problems and can also serve as a guide for basic science investigation. If successful, research for basic mechanisms could produce generic approaches to the control of diverse childhood injury problems and contribute to our understanding of human processes ever beyond the area of childhood injury.

METHODOLOGICAL ISSUES

Like all fields of investigation, child-hood injury research requires careful attention to the development and application of methodology. While some of the methodologic considerations for childhood injury are widely applicable to the conduct of research in many areas, others are more specific for injury control in the pediatric population. Some of these issues, such as study design, aggregation or segregation of data, and measurement, are briefly discussed in relation to specific concerns for the field of childhood injury research.

Study Design

Research in childhood injuries may be divided into several broad categories: description of occurrence, assessment of cause, and evaluation of interventions. These inquiries can be approached through a variety of study designs, each with its own set of problems and pitfalls.

The prospective cohort study in which the hypothesized cause is measured before the occurrence of the outcome can provide strong evidence for a causal relationship. However, because serious injuries are relatively rare events, prospective studies require large populations to be followed up over long periods. For example, prospective information on 100 children with injuries severe enough to result in hospitalization requires collection of data on about 12 000 children for one year. An alternative is to identify data sets collected for other purposes that have sufficient data on variables of interest to test hypotheses about the occurrence of injuries. For example, cohorts of British children born in 1958 and 1970 were originally followed up for the purpose of assessing outcome of obstetric practices, but detailed questions about injuries in the cohorts have allowed prospective analyses of the role of family structure,57 child behavior,58 child development, and social factors in relation to children's injuries. Unfortunately, detailed assessments relevant to childhood injury are rarely included in data collected for other research purposes.

Studies that assess the cause of injuries have relied heavily on the case-control design in which cases are typically users and controls are nonusers of health services for treatment of injuries. This design is particularly problematic for certain types of hypothesized risk factors, notably child behavior and maternal depression, as inference about whether such factors predated or resulted from the injury is clouded by the retrospective design. The selection of cases and appropriate controls is based on the underlying assumption that the prevalence of the causal agent or risk factor in the sample of cases is representative of its prevalence in the population of cases and likewise for controls. However, if the cause or risk factor is associated with access to health care or likelihood of admission to the hospital, then inference about the role of that factor can be seriously biased.

Studies to evaluate interventions present a number of important design choices. For example, the unit of analysis can be individuals, geographic entities, or institutions; the units can be randomly assigned to treatment, or natural experiments can be observed (eg. different safety regulations naturally occurring in different locales). The outcomes can consist of occurrence of injuries or, alternatively, of behavior logically or empirically associated with injury (eg. use of seat belts following institution of seat belt laws rather than injury rates following seat belt laws). These are but a few examples of the decisions and problems associated with research design in childhood injuries. However, expansion and increasing complexity of injury research demands meticulous attention to such issues.

Study Population and Generalizability

The goal of injury research is to be able to generalize from findings concerning a sample of children to a broader population. The more narrowly a study population is defined, the less generalizable the results will be. On the other hand, a broad definition of study subjects requires stratified analysis by subgroup, which, in turn, requires larger samples and makes data analysis more cumbersome. Thus, the researcher is often faced with choosing whether to lump or split subject groups, and the decision made fundamentally affects the validity and generalizability of the proposed study. Suggestions for ways to maximize the generalizability of the results of studies concerning childhood injuries are as follows59: First, standard definitions are needed for the most commonly used subgroups of the most frequently studied variables. Age is the most common and inconsistently grouped variable. The groupings that parallel usual vital statistics groups should be standard, and variations from such standards should best reflect stages of normal child development. Second, definitions of subgroups should not overlap. Third, inadequate description of actual and potential injury victims imposes major limitations on subgroup analysis because improvement in the definition of injury subgroups should be a high priority for childhood injury researchers.

Measurement

Regardless of how well designed and applicable a study may be, its contribution depends heavily on the quality of the measurements employed. Problems with measurement were identified as one of the most frequent shortcomings found in clinical research applications to the National Institutes of Health, Bethesda, Md. 50 and in a recent group of applications to NICHD for research in childhood injury. Reviewers for the childhood injury applications especially criticized the proposed use of instruments that had not yet been developed or for which properties of validity and reliability had not yet been assessed. It is hard to overemphasize the importance of careful attention to measurement methods for which a number of references provide guidance to investigators. 61-64 When available and appropriate, the use of measures with established properties can greatly facilitate injury research.

However, as investigation in the field of childhood injury strives to expand beyond description to defining mechanisms and testing interventions, researchers must also develop new methods for measuring relationships and precepts. State-of-the-art technology for data collection could be applied to investigations in childhood injury. For example, in some studies of obesity, investigators now utilize telemetry and computer technology to gather continuous quantitative measurement of activity.65 These and similar approaches might be applied to the field of childhood injury to study, for example, the relationship of child activity level to risk of injury or for surveillance of children and control of environmental hazards. Potential investigators are urged to explore innovative applications of technology in conducting research or prevention of childhood injury.

RESEARCH QUESTIONS

Given our current understanding of the causes of childhood injuries, many important questions remain if we are to effect reductions in mortality and morbidity. The following questions are suggested as possible lines of investigation within a behavioral orientation that are likely to result in significant advances:

- 1. How do children learn those behaviors that alter the rate and severity of childhood injuries? This broad question circumscribes several more specific issues. Which specific skills must be taught to reduce injuries? What factors affect compliance with these behaviors? For example, does playing with guns promote aggression and/or lead to firearm injuries in children? Does a "false sense of security" play a role in generating accidents? Why are teenagers so resistant to the use of seat belts?
- 2. What approaches influence parents and communities to recognize hazards and insist on safe products and environments? More specifically, why are some approaches effective in motivating change toward a safer environment and others are not? How can schools and the media be used most effectively for injury prevention? How can parents be stimulated to demand safe products and manufacturers be stimulated to respond appropriately?
- 3. By what means or mechanisms are various risk factors associated with increased injury and noninjury? More specifically, why are some populations at risk, and how can they be protected? What are the chains of events that result in injury? How do family emotional illness and substance abuse affect childhood injury?
- 4. How does development of the child and the interaction of the environment and family in relation to this development contribute to safety and/or injury? How can environmental design effect behavior to improve child safety?
- 5. What interventions to prevent childhood injuries are specific to individual communities? How can these needs be best identified and effective interventions developed?

RESEARCH METHODS

Progress in solving health and scientific problems has often had to await the development of critical techniques, such as ultrasound imaging for assessing the natural history of neonatal intracranial hemorrhage. Similarly, research in prevention of childhood injuries is hampered by the lack of methods needed to investigate many of the questions facing the field. Measures or other methods judged by workshop participants to be most needed are as follows:

- 1. Proxy and precursor measures for childhood injuries. The occurrence of serious injury is sufficiently low and heterogeneous, rendering it extremely difficult to study as an outcome; a model of serious injury would facilitate research. The investigation of mechanisms and interventions would be greatly enhanced by the identification of events that are easily measured and highly correlated with serious injury.
- 2. Measure of injury severity and outcome. A validated scale of severity of pediatric injury with regard to outcome would be useful for prioritizing prevention efforts, comparing experiences across settings, quantifying approaches to care, and expanding other quantitative approaches.
- 3. Measures of exposure to risk. Accurate estimates of exposure to risk are essential for evaluating and targeting interventions in high-risk populations.
- 4. Validity and reliability of self-reported data. Seat belt use has been shown to be seriously overreported of when compared with observational data, and yet reports of mothers' prenatal smoking behavior correlate well with biochemical measures of maternal smoking behavior. For use in childhood injury research, validity and reliability of report data must be carefully assessed.
- 5. Measures of environmental hazards. A reliable and standardized approach to identification of environmental hazards in a variety of settings is an essential first step for research into the many aspects of the interaction of environment and childhood injury.

COMMENT

The NICHD concurs with the workshop participants and previous reports⁶ that an agenda for productive research to reduce the death and disability from childhood injury should be formulated. Therefore, the NICHD plans to join other federal agencies,

including the Centers for Disease Control, Atlanta, and Bureau of Maternal and Child Health and Resources Development, with a progressive commitment of resources to facilitate the scientific investigation of the means to accomplish this goal. The NICHD has planned a staged and multifaceted initiative of research toward prevention of childhood injuries that includes a program of contracts to develop new methods for investigation of childhood injuries and a succession of requests for grant applications focused initially on further elucidation of the behavioral mechanisms of childhood injuries and subsequently on interventions aimed at preventing these injuries. This initiative should contribute to the gathering momentum of expanded and productive research toward prevention of childhood injuries. Such attention should generate increased quantity and quality of research activity, entry of investigators from various disciplines into the field of childhood injury, and expanded use of multiple and large sources of data. Through such efforts and changes, the workshop participants and the NICHD hope to witness a reduction in mortality and morbidity due to injuries among children. It is hard to imagine a more exciting and worthwhile adventure.

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Gunshot Wounds in Children Under 10 Years of Age

A New Epidemic

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 Before 1980 we had not treated any children with gunshot wounds who were younger than 10 years of age, but the number has increased dramatically each year since then. Thirty-four children younger than 10 years of age were treated for gunshot wounds from 1980 to 1987. Sociologic and epidemiologic data were assessed by a child-abuse team and police. Other studies have concluded that gunshot wounds in young children were usually caused by unintentional injury, child abuse, or neglect.1-7 From our present study we add a further, and very disturbing, category, that of attempted or intentional pediatric homicide. The children in this category were shot in retaliation for gang activities of their older siblings. This study demonstrates that the majority of our patients' childhood gunshot wounds were related to gang violence and retallation, the availability of handguns in the home, and child neglect. The prevalence of childhood gunshot wounds in the inner city is increasing dramatically.

(AJDC 1988;142:618-622)

The majority of childhood gunshot wounds involve significant morbidity, not only to the child but also to the family and society. The long-term physical, emotional, and psychologic sequelae when permanent injury results are immeasurable. Childhood gunshot wounds have become a major urban medical problem in the past decade.¹⁻⁷

Three recent studies have shown that the incidence of pediatric gunshot

wounds has increased dramatically during the past ten years.⁸⁻¹⁰ These studies included children up to 16 years of age and focused on the teenage group, in which the majority of shootings are related to gang violence.⁸⁻¹⁰ Only one study examined children in their first decade of life.¹ This study concluded that gunshot wounds in young children were usually caused by unintentional injury, child abuse, and neglect.

The epidemiologic and sociological factors involved in childhood gunshot wounds must be characterized and understood before preventive measures can be implemented. A study of all childhood gunshot wounds treated at the King/Drew Medical Center, Los Angeles, with prospective sociological follow-up was performed to characterize this phenomenon.

PATIENTS AND METHODS

A chart review based on computerized diagnostic coding (International Classification of Diseases) was performed on all patients younger than 10 years of age who sustained gunshot wounds and were treated in the emergency department between January 1974 and February 1988. Outpatients were identified by reviewing all of the emergency department records. We excluded children older than 9 years of age because this group had been previously studied and their wounds were found to have a much different set of causes than wounds in the present study group.

The data collected included age, sex, date, weapon used, shooter, location of incident, anatomical location of the wounds, whether or not the bullet was retained, treatment administered, complications, permanent sequelae, and disposition of the patients. Sociological and epidemiologic data were gathered by contacting the parents by telephone and letter, followed by

interviews of the patient and family by an investigator, a social worker, and members of the Suspected Child Abuse and Neglect (SCAN) team. The SCAN team also investigated each patient during hospitalization. Police were contacted in each instance to determine the official disposition and cause of the shooting, and whether or not criminal or neglect charges were filed.

The SCAN team consisted of an attending pediatrician, a pediatric fellow, a pediatric radiologist, a physician assistant, a social worker, a venereal disease control nurse, and a liaison officer for the medical center. If child abuse or neglect was suspected the SCAN team notified the Los Angeles County Child Protective Services Department, which in turn conducted a full investigation and took legal actions where appropriate.

The sociological and psychologic investigation included long-term follow-up of the patients to determine the adequacy of peer and family relationships and the child's adaptation to school.

RESULTS

The study hospital serves an innercity area of 100 square miles with a population of 2 million people. Review of the medical records from 1974 to 1987 showed that no child under 10 years of age was shot and hospitalized at the study hospital before 1980. Childhood gunshot wounds seem to be a new phenomenon in south-central Los Angeles.

Since 1980, there have been 34 gunshot wound victims 9 years of age and younger. Each patient was seen by the SCAN team and followed up by a social worker. Twenty-three of the patients' families received long-term follow-up by telephone, while only five families came for the personal interview by the researcher. All of the families were extensively interviewed by the SCAN

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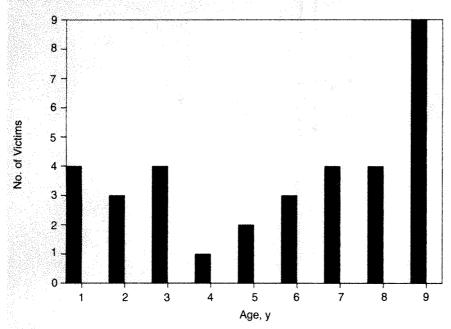


Fig 1.—Ages of gunshot wound victims.

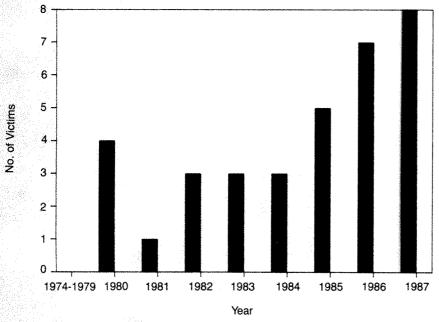


Fig 2.—Years in which gunshot wounds occurred.

team and police. Overall data on the cases are shown in the Table.

The mean age of the patients was 5.7 years (SD, 3.0 years) and the median was 6 years (Fig 1). The malefemale ratio was 16:18. The racial distribution included 21 blacks and 13 Hispanics, statistically approximating the distribution of the catchment area of the hospital. Figure 2 shows the increasing incidence of gunshot

wounds in children under 10 years of age seen at this hospital.

Shootings involved four BB guns, eight shotguns, six .38-caliber and 12 .22-caliber handguns, one larger-caliber handgun, and two high-velocity rifles (M-16). The gang retaliation shootings were done with low-velocity handguns. Sniping was done with M-16s. Shotguns and low-velocity handguns were used in family disputes

that resulted in accidental shooting of children. Data on the shooters are shown in the tabulation below.

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The mortality rate was 9%. There were two deaths in the emergency department: two 1-year-old children, respectively, sustained .38-caliber handgun and M-16 bullet wounds in the head. One 2-year-old child died in transit to the operating room of a .22caliber bullet wound in the head. This compares with a mortality of 3.1% for children 15 years of age and under,10 and 3% for children 15 years of age,12 who were treated at the same institution. Adult patients had mortality rates ranging from 0% to 3% depending on the area hit by low-velocity handgun bullets. 18-15

Of the 31 surviving patients, 46% had bullets retained at the site, and in 54% bullets were removed or exited at the time of injury. The average hospital stay was 11 days.

The following tabulation lists the anatomical locations of the wounds:

| | No. (%) of |
|-----------------|------------|
| Area Hit | Patients |
| Head | 13 (39) |
| Chest | 5 (15) |
| Neck | 4 (12) |
| Abdomen | 4 (12) |
| Lower extremity | 4 (12) |
| Upper extremity | 3 (9) |
| Eye | 1 (3) |

There were ten patients with long-term physical complications. These included three children with brain damage that required permanent skilled nursing care in a hospital, one child with recurrent bowel obstructions, two children with permanent colostomies, one child who lost an eye, two children with amputated fingers and hands, one child with a wrist drop from a radial nerve injury, and another with a subcutaneous abscess that required surgical drainage (one child had

| atient No./ Age, y/Sex | Area | Shooter (Age, y) | Reason | Complications | Time in Hospital, d | Disposition |
|---------------------------|-------------------|---------------------|-------------------------------------|-------------------------------|------------------------|---|
| 1/1/M | Head | Grandfather (46) | Family dispute, stray bullet | Died 3 d later | Death | Death/grandfather to prison |
| 2/2/F | Head | Gang (16) | Retaliation | Epidural hematoma | 20 | Rehabilitation |
| 3/2/M | Neck | Family (?) | Self-defense, stray bullet | Major surgery | 21 | Protective custody |
| 4/3/F | Neck | Gang (15) | Feuding, stray bullet | None | 8 | Protective custody |
| 5/6/F | Head | Robber (16) | Robbery | None | 6 | Home |
| 6/1/M | Head | Grandfather (46) | Family dispute | Death | Death | Death, grandfather in prison |
| 7/8/F | Chest | Gang (15) | Gang, mistaken identity | Severe brain damage | ••• | Permanent hospitalization required |
| 8/9/M | Leg | Gang (17) | Retaliation | None | 2 | Home |
| 9/3/F | Rectum | Brother (8) | Accidental, playing | Colostomy, surgeries | 22 | Home |
| 10/7/F | Arm | Self (7) | Accidental, playing | Infection, finger amputations | 8 | Home |
| 11/9/F | Neck | Cousin (7) | Accidental, playing | None | 6 | Home |
| 12/2/F | Head | Sniper (?) | Sniper | Death | Death | Death |
| 13/8/M | Face | Gang (?) | Gang war, stray bullet | Surgery, intubation | 15 | Home |
| 14/6/F | Head | Neighbor (36) | Shot at dog, hit child instead | None | 3 | Home |
| 15/5/M | Hand | Self (5) | Accidental, playing | Amputated hand | 12 | Home |
| 16/8/M | Neck | Unknown (?) | Stray bullet | None | 2 | Home |
| 17/9/M | Abdomen | Father (34) | Target shooting, hit by ricochet | None | 5 | Home |
| 18/9/F | Arm | Brother (12) | Accidental, playing | Infection, wound | 3 | Home |
| 19/9/F | Chest | Friend (12) | Accidental, playing | None | 3 | Home |
| 20/7/F | Eye | Gang (17) | Retaliation | Lost eye | 7 | Home |
| 21/7/F | Abdomen | Gang (16) | Retaliation | Frequent bowel obstructions | 7 | Home |
| 22/4/F | Buttock | Gang (?) | Stray bullet from gang war | None | 5 | Home |
| 23/8/M | Head | Robber (19) | Robbery | None | 1 | Home |
| 24/9/F | Head | Gang (?) | Retaliation | Infection, wound | 6 | Home |
| 25/9/M | Leg | Self (9) | Accidental | None | 4 | Home |
| 26/7/M | Abdomen, chest | Friend (9) | Accidental, playing | None | 7 | Home |
| 27/1/M | Head | Gang (15) | Retaliation | Brain damage | 28 | Home |
| 28/1/M | Head | Grandfather (50) | Family dispute | None | 6 | Protective custody |
| 29/3/M | Abdomen | Grandfather (64) | Family dispute, stray bullet | Surgery, colostomy | 21 | Protective custody |
| 30/3/F | Chest | Brother (5) | Accidental | Surgery | 7 | Home |
| 31/5/F | Chest | Gang (?) | Stray bullet | Surgery | 21 | Home |
| 32/6/M | Head | Self (6) | Accidental | Brain damage | 35 | Disabled permanently |
| 33/9/M | Face | Friend (11) | Accidental | None | 7 | Home |
| 34/9/F | Chest | Gang (19) | Retaliation | None | 20 | Home (both parents and uncle killed at same |

two long-term physical complications).

Seventy percent the shootings occurred outside the home. The cause of each shooting was categorized as one of the following: domestic violence, stray bullets from gang warfare, stray bullets from target practice, sniper fire, and gang retaliation. Gang retaliation occurred when one gang could not retaliate directly against a member of a rival gang and so intentionally shot the other gang member's easily accessible sibling.

Of the 27 children who were shot for reasons other than gang retaliation, only three were intended victims. Ten shootings were the result of domestic violence and the other four involved a missile intended for another target, as shown below.

| 맛입니다. 그런 바꾸다. 기타보다 | No. (%) of | | | |
|--------------------------|------------|----------|--|--|
| Reason for Shooting | Pat | Patients | | |
| Accidental/playing | | | | |
| with gun | 10 | (29) | | |
| Hit while gun was aimed | | | | |
| at another family member | 1 | | | |
| during a family dispute | 10 | (29) | | |
| Gang retaliation | 7 | (20) | | |
| Stray bullets, probably | | | | |
| gang related but not | | | | |
| intended to hit child | 4 | (12) | | |
| Shot during robbery | 2 | (6) | | |
| Sniper fire | 1 | (3) | | |
| | | | | |

Twenty of the patients were believed to be victims of child neglect, and the Los Angeles County Child Protective Services were notified. The guardians of these children were believed to have failed to provide a safe environment, and thus endangered the well-being and even the lives of the children. Judicial intervention occurred in each of these cases, and criminal actions were taken in three of them. Four children were placed in protective custody. All of the nine children who were followed up for as many as five years were apparently doing well, without physical or emotional handicap, and had adapted to peers and school life. The following tabulation shows the final disposition of all of the gunshot wound victims in the present study:

| Disposition | No. (%) of Patients |
|---------------------------|------------------------|
| Home | 24 (71) |
| Protective custody | 4 (12) |
| Permanent hospitalization | |
| required | 3 (9) |
| Mortality | 3 (9) |

COMMENT

Childhood gunshot wounds seem to be a new phenomenon in south-central Los Angeles. We classify gunshot wounds in the very young by the following causes: (1) unintentional injury; (2) child neglect; (3) child abuse; and (4) intentional attempts at homicide.

Ten children in the present study were unintentionally shot by other children or accidentally shot themselves. Heins et al1 also found that a common cause of childhood gunshot wounds was another child who found an easily accessible gun that was meant to be used for home protection. In a 1987 teenage gunshot wound study10 from the King/Drew Medical Center, 80% of victims were shot during gang-related activities. Four children in the present study were hit by stray bullets during gang shoot-outs. There were no hunting accidents, as the closest hunting ground is at least 100 miles away.

In only one of our 34 patients was child abuse the actual cause of the shooting. In 20 other cases the guardians were believed to have been negligent in the care of the child. Unintentional firearm injuries generally occur in or around a family dwelling,16 an observation that was confirmed by the present study. Watson¹⁶ noted that accidents "arise out of human interaction and human situations which are characteristics of our social system." Accident rates are highest in socioeconomically depressed urban areas, in part because of defective and unsafe housing and parental factors.17 Parents, because of illness, preoccupation, or disposition to action, may create situations that might lead to injury of their children.17

In today's society, in which family violence is a relatively common occurrence, ¹⁸ the child is often an unintended victim of domestic violence and may be shot as an innocent bystander. ¹⁹ There were ten such children in the present study. Steinmety ²⁰ reported in a national survey of domestic violence that a knife or gun was used in 4% of incidents of this type.

While much research has been done on teenage shootings, intentional homicide involving children younger than 10 years of age has not received much attention. Intentional gunshot wounds in the teenage group are often gang related; the victim and assailant are often acquainted. 1.8-16,21

Seven of our patients were reported by police to have been shot secondary to gang retaliation. One gang could not retaliate directly against a member of another gang; instead, an easily accessible sibling was shot while he was playing in the street. This phenomenon of childhood gunshot wounds has not been previously reported and has become significant since 1984.

Child homicide is not new, as infanticide and "overlaying" (taking the infant to bed and suffocating it with one's own body) were reported to be highly prevalent as long ago as 1250 AD.²² In victorian England, neonaticide was considered to be a common method of "birth control."²³ In 1980, the Federal Bureau of Investigation reported that 27 homicides of children under 10 years of age occurred in the United States.²³ Fatal child abuse was not calculated into this statistic.

Child homicide is often viewed as an extreme case of child abuse.24 Since 1925, homicide rates for children have increased sixfold.24 Childhood homicide is not a problem unique to the United States, but it is a greater problem here than in most other countries.24 Jason24 found that the homicide rates peaked in infancy and the teenage years. Overall, 35% of child homicides were perpetrated by acquaintances, 29% by parents, and 10% by strangers. As the victims' ages increased, the relationship between the victims and their assailants shifted from being intrafamilial to extrafamilial.24,25 At 3 years of age, the majority of homicides were committed by close relatives, and by 12 years of age homicides by acquaintances predominated.24 The incidence of homicides in which guns were used among children up to 18 years of age was 40%.24 Firearms are being used with increased regularity, and their use prevails in homicides at all ages,28-31 with an increase in use from 55% in 1960 to 67% in 1973.26 The present study confirms the rising incidence of gunshot wounds in children in the Los Angeles area.

Other studies1 have concluded that

gunshot wounds in young children were usually caused by unintentional injury, child abuse, and neglect. The results of the present study show that the majority of childhood gunshot wounds are the result of the availability of handguns in the home, as well as child neglect. Addressing these conditions through public education and social reform may help diminish this destructive "disease." From our present study we add a further, and

very disturbing, category, that of attempted or intentional pediatric homicide. The majority of these children are victims of street crime and gangrelated retaliation.

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In Other AMA Journals

ARCHIVES OF GENERAL PSYCHIATRY

Behavioral Inhibition in Children of Parents With Panic Disorder and Agoraphobia

Jerrold F. Rosenbaum, MD; Joseph Biederman, MD; Michelle Gersten, EdD; Dina R. Hirschfeld; Susan R. Meminger, PhD; John B. Herman, MD; Jerome Kagan, PhD; J. Steven Reznick, PhD; Nancy Snidman, PhD (Arch Gen Psychiatry 1988;45:463-470)

Characteristics of Fatal Gunshot Wounds in the Home in Oklahoma: 1982-1983

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• Children are a unique group at risk of injury from firearms because of their Immaturity, curiosity, and imitative behavior. All unintentional firearm deaths In persons younger than age 20 years that occurred in Oklahoma in 1982 and 1983 were reviewed. There were 32 unintentional deaths from firearms in children from birth to age 19 years. The death rate in rural counties was four times that of urban counties. Twentyseven deaths (85%) occurred at home. with an adult present in only two cases. The home death rate for males was 5.2 times that of females, with 15- to 19-yearold males most at risk. The rates among whites and Native Americans were simllar, at 1.5 and 1.2 per 100 000, respectively, with no deaths among the black population. This review concurs with previous studies that firearms are a significant cause of mortality in the pediatricage group. Counseling parents about the hazards of firearms may prevent deaths through better supervision and more responsible gun care and storage. (AJDC 1988:142:623-626)

Unintentional injuries are the leading cause of death among children and adolescents, accounting for greater than 50% of all deaths in persons 1 to 24 years of age. 1.2 In the United States, 22 000 children and youths from birth to age 19 years die of unintentional injuries each year. 3 Although the mortality rate for childhood disease has greatly decreased

over the years, the death rate from unintentional injury from 1964 to 1978 did not show a similar decrease in 1 to 19 year olds. While the death rate from unintentional injury decreased in the less than 1-year-old age group, it has remained fairly stable in the 1to 14-year-old age group, and increased slightly in the 15- to 24-yearold age group. Most injuries occur at home, where good safety habits should start. Defining the epidemiology of home injuries and the groups at highest risk for death from injuries may allow a clearer focus on more effective and efficient measures of preventing such deaths. This study examines the circumstances surrounding all home unintentional firearm fatalities in children from birth to 19 years old in Oklahoma during a two-year period.

METHODS

All fatal, non-motor vehicle, unintentional injuries in persons younger than age 20 years that occurred in Oklahoma in the calendar years 1982-1983 were reviewed by examining state medical examiner records. Oklahoma state law requires all nonnatural deaths to be reported to the medical examiner's office. Thus, all injury-related deaths should be recorded there. To verify this, the number of unintentional firearm deaths reported to the medical examiner was compared with the number of such deaths recorded on death certificates at the health department. Although 36 deaths from accidental gunshot wounds were recorded through the health department, 32 deaths were reported to the medical examiner, accounting for 89% of the total unintentional firearm deaths. Computer printouts from the medical examiner of all deaths coded as "accidental nonmotor vehicle" were obtained. These printouts also included the race, sex, age, county of death, presence of an adult, county of injury, and cause of death. Details about the circumstances of the injuries were also

noted from a narrative section of the medical examiner's charts.

Unintentional firearm deaths occurring at home were further examined. Home was defined as the house and immediate vicinity of the garage and yard. The age, sex, and race of the victim, the month and time of day of the injury, the presence of other people at the scene of the injury, and the county of injury were examined in further detail.

Population estimates were obtained from Oklahoma Health Statistics for 1982 and 1983, and Oklahoma Population Reports for 1980 through 1984. The proportion of persons by race, sex, and age was extrapolated from 1980 Oklahoma General Population Characteristics and 1980 Census Data.

RESULTS

In Oklahoma in 1982 alone, unintentional injuries accounted for 29% (411) of all deaths from birth through age 19 years, and 56% (385) of all deaths in 1 to 19 year olds. The largest percentage of these deaths in 1 to 19 year olds was due to motor vehicle accidents (34% [236]). Other unintentional injuries accounted for 22% (149) of deaths. The next largest group of fatalities was malignant disorders (15% [104]) followed by cardiovascular (8% [55]) and congenital anomalies (6% [42]).

In the calendar years 1982-1983, 277 unintentional non-motor vehicle accident deaths in persons from birth to age 19 years were reported to the state medical examiner. Of these 277 deaths, 50.5% (140) occurred in or around the home. The leading cause of home deaths were fires at 26% (36); followed by gunshot wounds, 19% (27); drowning, 15% (21); choking, 12% (17); poisoning, 9% (13); electrocution, 7% (ten); falls, 4% (five); and miscellaneous, 8% (11).

Firearms accounted for 32 fatal in-

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| | | Population From Birth | | |
|----------|--------|--------------------------|-------|--|
| Race | Deaths | to Age 19 y | Rate* | |
| White | 25 | 853 012 | 1.5 | |
| Native | | | | |
| American | 2 | 84 248 | 1.2 | |
| Black | 0 | 94779 | 0 | |

*Per 100 000 persons from birth to age 19 years each year.

juries, 27 of which occurred at home. All were classified as unintentional and not as homicide or suicide. Unlike other leading causes of injuries, there were no unintentional firearm deaths among the black population (Table 1). The rates of unintentional firearm deaths occurring at home among whites and Native Americans were similar, at 1.5 and 1.2 per 100 000, respectively.

The death rate in rural counties (population <75 000) was four times that of the urban counties (Table 2). Eighty-five percent (23) of the home unintentional firearm deaths were in rural counties. The rural counties had deaths in all age groups studied; however, the 5- to 9-year-old and 15- to 19-year-old age groups had the highest rates (Table 2). The home urban deaths involved white boys between the ages of 9 and 13 years.

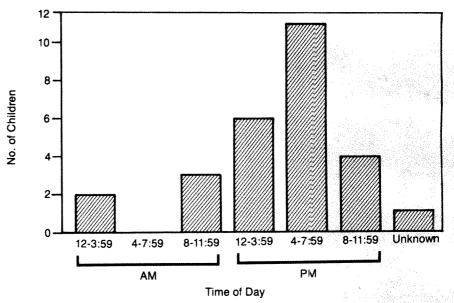
Firearms accounted for 36% (25) of all unintentional home fatalities in 5-to 19-year-olds. Males had a home firearm death rate over five times that of females (Table 2). The rates increased with increasing age for the males, whereas among the females, the 5- to 9-year-old age group had the highest death rate. The 15- to 19-year-old males accounted for 37% (ten) of the home firearm deaths. The female victims were all younger than age 9 years.

The majority of the unintentional firearm deaths occurred in the afternoon and evening hours, with 22% (six) occurring from noon to 3:59 pm and 41% (11) occurring from 4:00 pm to 7:59 pm (Figure). Seasonal variation was also present. Ten deaths (37%) occurred from September through November, followed by eight deaths (29%) from December through Febru-

Table 2.—Home Unintentional Firearm Deaths by Age, Sex, and County Population in Oklahoma: 1982-1983

| | | | No. o | Poeths (Rate*) | | |
|--------|-----------------|----|-------|----------------|-----------|----------|
| | | | Se | × | County Po | pulation |
| Age, y | Total, Overall | | M | F | <75 000 | >75 000 |
| 0-4 | 2 (0.4) | 1 | (0.4) | 1 (0.4) | 2 (0.7) | 0 |
| 5-9 | 9 (1.8) | 6 | (2.4) | 3 (1.2) | 7 (2.4) | 2 (1.0) |
| 10-14 | 6 (1.2) | 6 | (2.4) | 0 | 4 (1.4) | 2 (1.0) |
| 15-19 | 10 (1.7) | 10 | (3.2) | 0 | 10 (2.9) | 0 |
| Total† | 27 (1.3) | 23 | (2.1) | 4 (0.4) | 23 (1.9) | 4 (0.5) |

*Per 100 000 persons per year. †Ages from birth to 19 years.



Time of day of home firearm deaths in Oklahoma: 1982-1983.

Table 3.—Type of Gun Used in Unintentional Firearm Deaths in Oklahoma: 1982-1983

| | | Type of Firea | rm, No. (%) | |
|-------------|----------|---------------|-------------|---------|
| | Long Gun | Pistol | Pellet | Unknown |
| All deaths | 18 (56) | 11 (34) | 2 (6) | 1 (3) |
| Home deaths | 14 (52) | 10 (37) | 2 (7) | 1 (4) |

ary, five deaths (18%) from June through August, and four deaths (15%) from March through May.

Only two children (7%), were known to be with an adult at the time of injury. Eighty-five percent (23) were with a peer or sibling at the time of the shooting. The injury was self-inflicted in 22% (six) of the cases. The gun was fired by a friend in ten cases (37%) and by a family member, usually

a sibling, in nine cases (33%). Most of the injuries occurred while the children were playing with the gun (67% [18]). Eleven percent (three) of the injuries occurred while preparing for hunting or cleaning the gun. The child's activity was unknown in 14% (four) of the cases, and miscellaneous activities accounted for the remaining 7% (two). Fifty-two percent (14) of the wounds involved the chest, 44% (12)

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involved the head, and 4% (one) involved the abdomen.

Long guns were the most commonly involved in these home fatalities, with shotguns and rifles accounting for 52% (14) of the deaths; pistols, 37% (ten); pellet guns, 7% (two); and 4% (one), unknown (Table 3). The guns involved in the urban deaths were two long guns, one pistol, and one pellet gun. Blood alcohol levels were measured in 48% (13) of the home firearm victims. Only one victim, a 17-year-old male, had a positive blood alcohol test result.

COMMENT

Oklahoma is a predominantly rural state, which may make it difficult to generalize our data to other areas of the United States. However, being cognizant of the circumstances surrounding unintentional firearm fatalities in different social and geographic settings is a necessary step in dealing with this problem.

Previous studies have noted that firearms are the third leading cause of unintentional injury for 10 to 19 year olds, and in Oklahoma this was also true.⁵ The percentages of unintentional firearm fatalities occurring in the home have ranged from 56% to 93% in other studies, which are consistent with our finding that 85% of the deaths occurred at home.⁶³

One in five households in the United States has been estimated to contain a handgun, with 38% to 50% of all households containing some type of firearm.9 Furthermore, Patterson and Smith found that 55% of these families reported that the gun was loaded at all times and that half of the loaded guns were not locked away. Children often do not realize the gun is loaded or may not make the distinction between toy and real guns. 8,10 There were at least four cases in our review where the child or adolescent did not know the gun was loaded, or assumed it was not, since the gun was "never loaded." At least three guns were kept loaded under mattresses, and one loaded rifle was kept under a child's bed.

Protection of family and home is the most common reason given for owning a firearm. 6.8.9 However, a loaded firearm in the home has been found to be six times more likely to cause an un-

intentional death than the death of an intruder. Furthermore, it has been found that homeowners thwart fewer than five burglaries in 1000 by shooting the intruder.

Males were at much higher risk for injury in our study, as has been found in other studies. 7,8 Some studies have found blacks overrepresented in firearm fatalities, while others have found the majority of deaths to be among whites.7,11 A similar discrepancy is noted when looking at rural vs urban settings.9,11 It has been suggested that poverty, rather than race or population density, is the common element in the prediction of gunshot death in children.11 Our study revealed a preponderance of fatalities in rural areas, and there were no deaths in the black population. Oklahoma is a predominantly white, rural state so the lack of deaths among blacks may be chance. The small number of deaths in the urban counties may be because the perceived need for self-protection with handguns is less than that in other larger urban areas. Other studies have reported that handguns are involved in over half the unintentional firearm deaths. 7,8 In contrast, our study found long guns to be the most frequent type used, which again may be related to Oklahoma's rural population.

Other studies have found that approximately 40% of the unintentional firearm fatalities in children younger than 15 years old were self-inflicted. which is a higher percent of self-inflicted injuries than we found. 7.8 It may be difficult to determine who actually fired the gun in injuries involving children. The peer involved in the shooting death of a friend or sibling may have problems coping with feelings of guilt and perhaps fear and may not give accurate details about the events of the injury. Of interest, at least four boys in our study invented stories, usually blaming someone else. that they eventually changed. In one case of triplets playing with a gun, the two surviving triplets initially made up a story that a "masked man opened the door into the living room and fired." Friends and family members will need extra attention in resolving any emotional problems these children may be encountering.9,10

Our findings concur with others that most home firearm injuries occur when the child is playing with the gun. 6.7 Numerous firearm injuries have occurred when a child imitates a scene he has seen on television. 10 Two groups of boys in the 10- to 14-year-old age group in our study were involved in games consisting of loading and pointing the gun in a contest to see who could do it fastest.

Older boys may play with nonpowder firearms. Although they are often considered toys and are usually used by children younger than age 15 years, they can cause serious injuries also. ¹² Two deaths in our study were from pellet gun injuries.

This study looked at fatalities, but the morbidity from unintentional gunshot wounds is even greater. Unintentional firearm injuries claim 1200 to 1500 children's lives each year, with an additional occurrence of 8000 nonfatal injuries. Preventive measures would not only decrease the number of deaths due to injuries but could also greatly decrease nonfatal injuries.

Suicides and homicides were not examined in this study, even though the distinction between these deaths and unintentional deaths may not always be clear. Making guns less accessible to children and adolescents may also decrease the number of deaths from firearm suicides and homicides. Suicides and homicides are usually inflicted with whatever is most available. Since firearm injuries have a very high case fatality rate, making firearms less available could replace these fatalities with less serious injuries. 18

Pediatricians, who have historically been leaders in preventive health care, can take an active role in injury prevention. Eliminating firearms from the environment of children and adolescents is the safest preventive measure. However, as long as people own guns, other firearm safety precautions can be followed. Questions about firearms could be raised by physicians during routine health visits. He American Academy of Pediatrics has suggested that the following rules for firearms in the house be discussed: (1) never keep a loaded gun in the house

or car; (2) keep gun and ammunition locked in separate places; (3) always treat a gun as if it were loaded and ready to fire; (4) never allow children access to guns; and (5) have a gunsmith check antique and souvenir guns to be sure they are not loaded and fix these guns so they cannot be fired. The recommended safety precautions for

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the field that could also pertain to the home are (1) know how to operate and clean a gun before loading it; (2) never point a loaded gun at anyone; (3) always unload a gun before setting it down; (4) disengage the barrel of the gun before passing it to another person; (5) handle a gun so that the muzzle can be controlled in the event of stumbling or falling; and (6) keep the safety catch on, but do not rely on it for safety.¹⁴

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CORRECTION

Incorrect Data.—In the PEDIATRIC FORUM entitled "An Eight-Variable Clinical Assessment Model for the Prediction of Cervical Spine Injury in Children" by Binns et al, published in the December 1987 issue of AJDC (1987;141:1249), the authors wish to correct their data. In paragraph 2 of the "Patients and Methods" section, the second sentence should have read as follows: "Either or both clinical predictors were present in 30 [not 26] children (51% [not 44%]) in our sample."

Pilot Evaluation of Instructing Parents of Newborns About Poison Prevention Strategies

Jessica M. Cooper; John A. Widness, MD; John S. O'Shea, MD

 Providing new parents with both written and verbal information about polsons and with syrup of ipecac appeared to be successful when distributed at discharge of their normal newborns. New parents who received neither Information nor ipecac served as controis. Distribution occurred during a nine-month period, which was followed after an interval of three months by a four-month evaluation period. The average (±SD) time between infant poison exposures and parent telephone calls to the statewide poison center during the evaluation period was 5±3 minutes for the subjects and 12 ± 4 for age-matched and socioeconomically matched controis. Both groups had similar frequencles of potentially dangerous exposures for which syrup of ipecac was recommended. Subject parents appeared to have homes which in various respects were significantly more child-safe than those of the controls. Significantly more control homes contained syrup of ipecac after the exposures than before (77% vs 41%).

(AJDC 1988;142:627-629)

Accidental ingestion of toxic substances continues to be a major pediatric problem. In the United States poisonings account for more than 4700 deaths annually. The annual incidence of nonfatal poisonings in children exceeds 1 million, most often in children less than 6 years of age.

Attempts that have been made to reduce the morbidity and mortality include legislative requirements for childproof packaging,² creation of the

National Clearinghouse for Poison Control Centers (now disbanded) and of regional poison control centers,³ and public education using various media. These measures have been associated with declines in the ingestion/general population ratio from 5.7/1000 in 1973 to 3.4/1000 in 1978, and in the fatality/population ratio from 2.1/100 000 in 1963 to 0.5/100 000 in 1980.

In the mid-1960s the Food and Drug Administration approved syrup of ipecac for over-the-counter availability as a safe and effective emetic to be used as medically directed for toxic ingestions. Fluid extract of ipecac, which is 14 times more potent than the syrup and is quite toxic itself, is no longer available in the United States. Syrup of ipecac bottles are labeled with the admonition that the syrup should not be given until after a physician or poison center has been consulted, since ingestion of some toxins may be worsened by the induction of vomiting (eg, alkali-containing products and some hydrocarbons).4 Syrup of ipecac has been recommended to be on hand at home by the American Medical Association, the American College of Emergency Physicians, the American Academy of Pediatrics, and the American Association of Poison Control Centers, and in editions of pediatric textbooks.1,5 For many drugs, studies in adults have shown that intervals from ingestion to evacuation of longer than 30 minutes are not conducive to successful gastric emptying.^{3,6} Some reports have also suggested that the cost of medical services can be substantially reduced with availability of ipecac in the home and telephone contact of a physician or poison center after an exposure. 8,6,7

The Rhode Island Poison Center, Providence, responds to 19000 calls per year. Approximately 15% of these calls result in a recommendation for gastric evacuation; 60% to 70% of such patients are younger than 6 years of age.

We sought to determine if provision of poison prevention instruction and syrup of ipecac to parents of newborns might decrease the severity and time to treatment after poisoning episodes.

SUBJECTS AND METHODS

For nine months beginning in the spring of 1985, 1-oz bottles of syrup of ipecac were distributed the day before discharge to all of the 5264 families of normal infants born at the Women and Infants' Hospital of Rhode Island, Providence (Figure), These parents also received a set of instructions on "poison proofing" their homes and the actions to be taken in the event of a poisoning. Standardized verbal instructions were given by the nursing staff, along with information sheets in the language spoken by the family. No similar programs were conducted during this period at any other hospitals in the Rhode Island area, from which a total of 4484 normal newborns were discharged during the same nine months. The overall socioeconomic distribution of families at Women and Infants' Hospital is similar to that of all other area hospitals combined (W. Hollinshead, P. R. Simon, unpublished data, 1986).

For the four-month period beginning 12 months after the start of the distribution period, all calls to the Rhode Island Poison Center were studied that involved children between 3 and 16 months of age. Within one month of each poisoning encounter, the homes of 92% of all such patients were contacted (ie, all with telephones and with at least one English-speaking parent in residence) and a standard questionnaire was administered. The following items were elicited: when and where the patient was born; parental knowledge of poison prevention strategies; and any apparent misuse of ipecac. Data for patients who had been born at Women and Infants' Hospital

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From the Division of Ambulatory Pediatrics, Rhode Island Hospital (Ms Cooper and Dr O'Shea), the Department of Pediatrics, Brown University (Ms Cooper and Drs Widness and O'Shea), and the Department of Pediatrics, Women and Infants' Hospital of Rhode Island (Dr Widness), Providence, RI.

during the distribution period were compared with those for patients born elsewhere in the state during the same period. During this postdistribution evaluation period the mean age of the subjects and controls was 9.5 months.

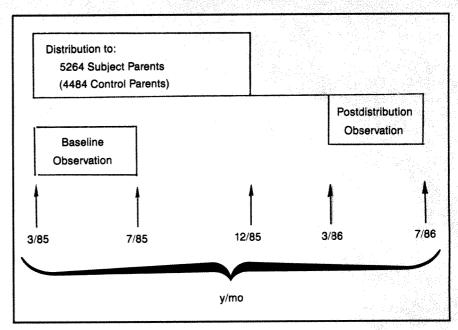
All data were analyzed for statistical significance by two-tailed t testing or by χ^2 determinations, with Yates' correction applied as indicated.

RESULTS

Only six children between 3 and 16 months of age (of the approximately 5264 whose parents had received the poison instructions and syrup of ipecac) and for whom syrup of ipecac was recommended had their toxic exposures reported to the Rhode Island Poison Center. Two calls were received from the group of 4484 similar children whose parents had not received either instructions or syrup of ipecac when their children were born elsewhere (P was not significant). None of these subject or control patients were younger than 6 months of age. The mean (±SD) time between exposure and contacting the Rhode Island Poison Center, however, was 12 ± 4 minutes for the two control patients and 5 ± 3 minutes for the other six patients (P<.01). None of the patients were judged to have become symptomatic from poisoning at the time that the ingestion was reported to the center, and none of these children were hospitalized.

During the same four months of the previous year a total of 18 calls were received by the poison center concerning children between 3 and 16 months of age for whom syrup of ipecac was recommended. Only eight such calls were received, however, during the four months of postdistribution assessment. For both years the number of births remained at approximately 13 000.

The homes of the six subject patients where syrup of ipecac was recommended were compared by telephone interviews with the homes of 22 age-matched control patients having poison encounters during the same period. At the time of toxic exposure, all six subject homes had available syrup of ipecac from the same lots distributed at the hospital, but only nine (41%) of the other 22 homes had



Study design. Postdistribution and baseline observations were compared for subject and control parents.

any syrup of ipecac. Within one month following the poisoning 17 (77%) of the control homes reported having ipecac available (P < .02 for improvement).

All of the six subject parents were able to describe properly the function of ipecac, as were 19 (86%) of the 22 control parents. Although all subject parents contacted the poison center before using syrup of ipecac, two of the control parents (9%) used syrup of ipecac prematurely, a difference found not to be significant (P>.05, power >.50).

When compared with subject parents (all of whom reported that they usually kept medicines, cleaning products, and alcoholic beverages separated from their children) only eight (22%) of the 22 control homes reported having child-resistant closures on their medicine cabinets (P<.01). Fifteen (68%) of the 22 control parents reported keeping cleaning products in closed containers (P<.05), and only seven (32%) kept alcoholic beverages inaccessible (P<.01).

The estimated cost of the distribution program per child was \$3.35: \$1 for an individual container of syrup of ipecac, 20¢ for printed poison instructions, and \$2.15 for personnel (one half-time nurse dealing with the parents of 5264 newborns over nine months).

COMMENT

It appears from the results of the present study that distributing poison information and syrup of ipecac to parents of newborns is at least somewhat effective in improving the response of parents to subsequent exposures. In contrast with control parents, the subject parents whose experienced exposures children treated with syrup of ipecac were more likely to have this drug available and contacted the poison center for advice more quickly. These parents reported approximately the same number of exposures as the controls, however, and their more rapid response time may not be clinically important. The subject parents may have been encouraged to report encounters of less severity than the controls, because of the emphasis on poison prevention they had received at the hospital. These parents claimed to have greater "poison proofing" in their homes when interviewed by telephone within one month after their children were involved in toxic exposures. To what extent these improvements could be confirmed would be worthy of study, as would the effect of older siblings in the household.

Even though there was a decline by 56% in calls where syrup of ipecac was

recommended over the two observation periods, this difference in advice to use ipecac may be due more to gradual, subtle changes in center policies than to any real change in the number of poison encounters. The total population served by the poison center did not change during the study, nor did the number of calls regarding patients of various ages.

The relative value of verbal poison instruction, compared with written instruction and with the actual distribution of syrup of ipecac, seems worthy of future study both soon after birth and probably following a poisoning incident. Future poison prevention

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approaches might then become more sharply focused, both to minimize expense and to avoid dependence on an unwieldy number of health care personnel for implementation. Similarly, the particular periods in their children's development or the circumstances when parents themselves are particularly receptive to poison prevention instruction should be delineated. For example, in the present study it seemed that parents might be particularly receptive the day before going home with a new baby or during the month after an exposure was reported. Finally, with the efficacy and safety of the widespread in-home pres-

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ence of syrup of ipecac currently under question, perhaps alternative strategies for minimizing poison morbidity could be substituted (eg, activated charcoal).

We thank Sumbal Ahmada of Wyeth Laboratories, Philadelphia, for syrup of ipecac, as well as Philip N. Johnson, PhD, and Dennis W. Welch, associate and assistant director, respectively, Rhode Island Poison Center, Newport, for identification of children with reported toxic exposures. Appreciation is also due to reviewers William J. Lewander, MD, medical director, Rhode Island Poison Center, Peter R. Simon, MD, MPH, Division of Family Health, Rhode Island Department of Health, and Leo Stern, MD, professor and chairman of pediatrics, Brown University, Providence.

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in Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Asbestos Bodies in Children's Lungs: An Association With Sudden Infant Death Syndrome and Bronchopulmonary Dysplasia

Abida K. Haque, MD, Mary F. Kanz, PhD (Arch Pathol Lab Med 1988;112:514-518)

Ethyl Alcohol (Ethanol)-Containing Cologne, Perfume, and After-shave Ingestions in Children

Deborah L. Scherger, RN; Kathleen M. Wruk, RN; Kenneth W. Kulig, MD; Barry H. Rumack, MD

· Colognes, perfumes, and aftershaves containing ethyl alcohol (ethanoi) are frequently ingested by children. These products may contain from 50% to 99% ethanol. To determine if ingestion of colognes, perfumes, or after-shaves by children results in serious ethanol toxic reactions, this retrospective study was performed. One hundred twentythree cases of children younger than 6 years old who ingested these products were reviewed. The cases were arbitrarily divided into three groups based on the amount ingested by history. Group 1 included children in whom less than 30 mL was ingested; group 2, 30 to 60 mL was ingested; and group 3, more than 60 to 105 mL was ingested. Of the 102 patients in group 1, no children experienced symptoms or signs. One of 17 children in group 2 was described by parents as sleepy but was asymptomatic one hour later. Two of four children in group 3 behaved as if intoxicated, yet blood ethanol levels were undetectable within 21/2 hours after ingestion. Based on our study, asymptomatic children who ingested by history less than 105 mL of a cologne, perfume, or after-shave and remain asymptomatic can be safely watched at home. All children with symptoms of intoxication need health care facility referral.

(AJDC 1988;142:630-632)

Ingestion of ethyl alcohol (ethanol)—containing cologne, perfume, and after-shave is common in children younger than 6 years of age. In 1985, there were 16589 exposures reported to the American Association of Poison Control Centers National Data Collection system, with 15593 involving children younger than 6 years of age. No

deaths were reported, and only two cases reported major effects.1

Because most of these products contain 50% to 90% ethanol, there is concern about serious intoxication when accidentally ingested by children. Although the literature provides management guidelines for ethanol exposures, these guidelines do not specifically address accidental ingestion of these ethanol-containing products. Treatment may be based on the amount ingested by history or on the calculation of the predicted peak ethanol level. This retrospective study was performed to determine the incidence and type of symptoms developing after pediatric ingestion of ethanol-containing cologne, perfume, and after-shave.

PATIENTS AND METHODS

A retrospective study involving children younger than 6 years of age ingesting ethanol-containing cologne, perfume, or after-shave and referred to the Rocky Mountain Poison and Drug Center, Denver, was performed. The study period was from Dec 1, 1984, to Jan 14, 1985 (a six-week period during the holidays). The 123 cases collected were arbitrarily divided into three groups based on the amount of product ingested by history. Group 1 included patients in whom less than 30 mL of the product was ingested by history; group 2 ingested 30 to 60 mL by history; and group 3 ingested more than 60 to 105 mL by history. Registered nurses ascertained the amount ingested by history from an adult caller. The amount the bottle contained when full minus the amount previously used minus the amount left determined the possible amount ingested. There were no cases in which more than 105 mL of the product was missing. Patients who could not be followed up by telephone were excluded from the study.

Each patient was analyzed for the following elements: (1) presence of symptoms, (2) induction of emesis, (3) referral to a

health care facility (HCF), (4) length of follow-up, (5) predicted peak ethanol level, (6) measured ethanol (if done) level, and (7) outcome. All children with symptoms of intoxication (drowsiness, ataxia, slurred speech) were referred to an HCF. The registered nurse treating the patient recommended induction of emesis or referral to an HCF based on the history of the amount ingested, symptoms, or the presence of dangerous coingestants.

The treatment the child received was determined by the treating physician at the HCF. Length of follow-up was determined by the symptoms present, if emesis was induced, or if the child was referred to an HCF. The predicted peak ethanol level was calculated by the following formula: $dose \times 0.79$ (specific gravity of ethanol) = Cp (serum ethanol level) × volume of distribution (0.6 L/kg for ethanol) × weight in kilograms. If the child's weight was not recorded, a mean weight chart for age and sex was used.

RESULTS

Of the 102 patients in group 1, one child received ipecac, no children experienced signs or symptoms, and no children were referred to an HCF. The mean length of follow-up for group 1 was two hours (range, one to 19 hours) (Table 1).

Of the 17 patients in group 2, six children received ipecac. One child in group 2 was described by parents as "a little more sleepy" 22 minutes after the exposure. The Poison Center recommended HCF referral and the parent declined. One hour later the child was described by mother as "normal." Two patients in group 2 were seen in an HCF. In the first case, the Poison Center had recommended ipecac-induced emesis for the child. The parent took the child to the HCF, and the child experienced no symptoms. In the second case, the Poison Center had recommended HCF referral because the child had ingested a potentially

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| Ī | | Tal | ole 1 | -Summa | ry of Data for | Three Gro | ups | |
|---|-------|---------------------------------------|-------|--------|-----------------------|---------------|-----------------|---|
| I | Group | Amount of Product Ingested, ml. | n | lpecac | Signs and Symptoms | Onset, min | Sent to HCF* | Mean Length of Follow-up, h (Range) |
| Γ | 1 | <30 | 102 | 1 | 0 | | 0 | 2 (1-19) |
| 1 | 2 | 30-60 | 17 | 6 | 1 | 22 | 2 | 4 (1-17) |
| 1 | 3 | >60-105 | 4 | 1 | 3 | 0, 30, 45 | 3 | 3 (1-5) |

^{*}HCF indicates health care facility.

| Tal | ble 2.—Predicte | d Peak i | and Measured | Ethanol Levels for | Three Groups |
|-------|---------------------------------------|----------|-----------------------|---|----------------------------------|
| Group | Amount of Product Ingested, ml. | n | Signs and Symptoms | Mean Predicted Peak Ethanol Level, mg/dL (Range) | Messured Ethanol Level, mg/dL |
| 1 | <30 | 102 | 0 | 99 (3-274) | |
| 2 | 30-60 | 17 | 1 | 351 (152-588) | * * * |
| 3 | >60-105 | 4 | 1 | 843 (542-1067) | 0 |

| Table 3.—Co Colognes, | ontents of Pe and After-sh | |
|--------------------------|-------------------------------|-----------------|
| | Ethanol | Perfume Oils |
| Perfume, % Cologne, % | 50-99 50-97 | 1-25 0.5-15 |
| After-shave, % | 15-90 | 0.8-8 |

toxic amount of aspirin in addition to the after-shave. Neither child experienced symptoms. The mean length of follow-up in group 2 was four hours (range, one to 17 hours) (Table 1).

Of the total of four patients in group 3, one child received ipecac. The Poison Center had recommended ipecacinduced emesis at home but it was unavailable. The parent took the child to an HCF for emesis induction. The child experienced no symptoms. Three children in group 3 were described as having symptoms. The first child vomited spontaneously, had no symptoms of intoxication, and was asymptomatic one hour after exposure. The second child was described by the parent as ataxic and having slurred speech 30 minutes after the exposure. The Poison Center referred the child to an HCF. The third child was described by the parent as "bumping into walls" and having slurred speech 45 minutes after exposure. The Poison Center referred the child to an HCF. The two children in group 3 who were referred to an HCF had undetectable

measured ethanol levels 2½ hours after exposure and received no specific treatment. The mean length of follow-up in group 3 was three hours (range, one to five hours) (Table 1). The mean predicted peak ethanol level for group 1 was 99 mg/dL (range, 3 to 274 mg/dL); for group 2, 351 mg/dL (range, 152 to 588 mg/dL); and for group 3, 843 mg/dL (range, 542 to 1067 mg/dL) (Table 2).

COMMENT

The distinction among a cologne, perfume, and after-shave is primarily in the percentage of perfume oils and ethanol they contain. After-shaves may also contain small concentrations of emollients and rubefacients. No precise definition or formula for what constitutes a cologne, perfume, or after-shave exists. They are similar in content, with ethanol being the primary ingredient (Table 3)2 (oral communications, Dr Gene Frank, Department of Research and Development, Beecham Cosmetics, Bensenville, Ill, July 1985, and Lucille Van Baaren, Department of Toxicology and Regulatory Affairs, Avon Products, Suffern, NY, July 1985).

The perfume oil component of these products generally consists of an essential oil or fragrance. Special denatured ethanols, excluding methyl alcohol, make up the ethanol component. The Bureau of Alcohol,

Tobacco, and Firearms regulates the types of denatured ethanols that manufacturers can use in these products² (oral communication, US Government, Treasury Department, Bureau of Alcohol, Tobacco and Firearms, Washington, DC, July 1985).

Ethanol is rapidly absorbed from the gastrointestinal tract, 20% in the stomach, and 80% in the small intestine.3 Peak blood ethanol concentration is achieved 30 to 60 minutes after ingestion. Food in the stomach or drugs (eg, anticholinergics or sympathomimetics) delay ethanol absorption4,5 and can prolong the peak concentration time from one to three hours. 4.5 Ethanol is primarily metabolized in the liver (90%) by alcohol dehydrogenase. A small percentage is eliminated unchanged by the kidney and lungs (5% to 10%).8,4,6 Traditionally, ethanol's elimination has been explained by zero order (linear) kinetics where the rate of ethanol oxidation is constant regardless of its concentration. Recent studies have disputed this and have suggested that nonlinear kinetics are involved. 7.8 The rate of elimination of ethanol in adults varies from 10 to 50 mg/dL/h and in children it may be more rapid (in one series the average elimination for children was 28.4 mg/dL/h).4.9

Ethanol toxicity in children is well described in the literature.9 Several cases of toxicity in children following ingestion of ethanol-containing mouthwashes (14% to 29.9% ethanol) have been reported, including one death. 10-12 Ethanol produces a central nervous system toxicity, including emotional instability, motor incoordination, ataxia, and, at higher doses, lethargy, obtundation, and coma. Gastrointestinal irritation may result in nausea and vomiting. Hypothermia occurs secondary to peripheral vasodilation and central nervous system depression. Hypoglycemia is a serious complication of acute ethanol intoxication in children and chronic alcoholics and, in some cases, may be delayed. Metabolic acidosis may also occur. Death usually results from respiratory failure.4,11

Blood ethanol concentrations are generally consistent with clinical symptoms. Chronic alcoholics usually tolerate higher levels than children and abstainers. With blood ethanol concentrations less than 50 mg/dL, it is unlikely that symptoms will occur. Blood concentrations of 150 to 300 mg/dL result in mental confusion, ataxia, exaggerated emotional states, changes in perception, and muscular incoordination; concentrations greater than 300 mg/dL result in stupor, blurred vision, and marked muscular incoordination; and deaths have been reported with concentrations above 400 mg/dL. The substantial lethal dose of ethanol in adults without supportive therapy is 5 to 8 g/kg and for children 3 g/kg.^{8,4,10}

Given the known toxic effects of ethanol and the predicted peak ethanol value for each group in this series of patients, symptoms and elevated serum ethanol levels would have been expected in a majority of the children. Possible reasons that may account for the absence of symptoms include an inaccurate history of the amount ingested or delayed absorption of the product. The history of the amount

ingested may have been inaccurate because the parent could not remember the exact amount of product available before the exposure. It is also difficult to ascertain the amount of liquid spilled in exact measurements. The child may not have ingested the amount missing because of the taste. If the child did ingest the product, absorption may have been delayed by food or medication in the stomach, decreasing the peak ethanol level and symptoms seen. These reasons may also account for the discrepancy between measured and mean predicted peak ethanol levels in the two patients whose serum ethanol levels were reported.

Our retrospective study did not address the efficacy of ipecac, lavage, activated charcoal, or cathartics. Because peak concentrations of ethanol can be achieved within 30 to 60 minutes, induction of emesis may be hazardous, as the emetic response (20 to 30 minutes after administration) may coincide with the central nervous system depression seen following signifi-

cant ethanol ingestion. It is uncertain if lavage or administration of activated charcoal and a cathartic would be effective, as ethanol is so rapidly absorbed. Although charcoal has been shown to significantly inhibit absorption of ethanol in experimental animals, is it has not been efficacious in preventing absorption in humans. 14

CONCLUSION

Based on the results of our study, children who ingest by history less than 105 mL of an ethanol-containing cologne, perfume, or after-shave and remain asymptomatic can be observed at home. Ingestions of greater than 105 mL were not examined in this study. Home treatment can be done safely only if there were no other products ingested by history, if home observation can be accomplished by a responsible adult, if follow-up by the Poison Center can be done easily, and if an HCF is readily accessible. All children experiencing symptoms of intoxication need an HCF referral.

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CORRECTION

Omission.—In the Ambulatory Pediatric Association Program and Abstracts, published in the April issue of AJDC (1988;142:365-408), the name of an author was omitted. On pages 374 and 395, in the abstract entitled "An AIDS Day-care Center: The First 18 Months," and by-lines should have read as follows: "H. M. Adam, A. P. Mezey, B. Weiss, and A. Rubinstein" (p 374); and "H. M. Adam, A. P. Mezey, B. Weiss, A. Rubinstein" (p 395).

Fatal Pepper Aspiration

Stephen D. Cohle, MD; John D. Trestrail III, RPh; Michael A. Graham, MD; David W. Oxley, MD; Barry Walp, DO; Joseph Jachimczyk, MD

 Eight patients (five previously undescribed) died due to aspiration of pepper. Seven deaths involved homicides, and one death was accidental in a child with documented pica. The pepper was administered by the mothers in three children and by a foster mother, the mother's boyfriend, an adult male friend, and the child's godfather in one case each. Homicidal pepper aspiration shares many of the features of more conventional child abuse: in each instance, the child was being punished, four of the seven assaliants initially gave incorrect histories, and four children were chronically abused. The facts that each death occurred in a different state and that five of the seven homicides occurred within the two years preceding the preparation of this report suggest that this form of child abuse is not confined to any single part of the country and may be increasing in frequency.

(AJDC 1988;142:633-636)

Reported cases of asphyxia by pepper aspiration are few, with only one case published before 1986.1 In the recent past, five additional unpublished cases have been recognized, and these cases, plus a review of the three published cases,1-3 form the basis of this report. Nearly all cases of fatal pepper aspiration are homicidal; a complete medical history and autopsy identified the lone accidental death.

PATIENT REPORTS

Patients 1 (from Ohio), 2 (from Michigan), and 8 (from Massachusetts) have been previously described, and their case summaries are given in the Table.

PATIENT 3 (From Virginia).—The mother of this 21/2-year-old girl admitted that she poured pepper down the child's throat as punishment for removing an infant sibling's bottle. The child was taken to a local hospital where attempted intubation was unsuccessful. The tip of the endotracheal tube was covered with black pepper when it was withdrawn.

The autopsy revealed multiple abrasions and contusions of different ages that involved the face, upper extremities, chest, back, buttocks, and lower extremities. Internal examination revealed occlusion of the larynx, trachea, and primary and secondary bronchi by pepper. The stomach was packed with large quantities of black pepper that extended into the first portion of the duodenum. The gastric mucosa was hyperemic.

PATIENT 4 (From Missouri).—This 5month-old male infant was found by his mother as he was choking on black pepper. The mother said that she had stepped out of the room for a moment and that the child had apparently ingested pepper from a shaker that she had left on the floor. Approximately ten minutes later, the child arrived at a local hospital emergency room. He was pronounced dead approximately 40 minutes later. Scene examination revealed vomitus that contained black pepper in two locations in the apartment. The pepper shaker was clean and contained no moisture. It was approximately one fourth full. All the perforations in the chrome top were patent, and the top was on the shaker. The pepper container in a nearby cabinet was empty. The mother subsequenty confessed to putting pepper in the child's mouth. She had also put pepper on his fingers to discourage him from putting his fingers in his mouth.

Pertinent autopsy findings revealed a few grains of pepper in the aryepiglottic folds. Beginning at 0.5 cm below the vocal cords, the larynx was occluded with black pepper, which extended into the right and left main-stem bronchi and some of the distal bronchi. The estimated volume of pepper was 12 mL.

PATIENT 5 (From Texas).—This 21/2-

year-old boy was in the presence of the mother's boyfriend when the child became unresponsive. The boyfriend stated that the child had poured pepper into his own mouth. The mother stated that the boyfriend frequently would beat the child for real or imagined offenses. In the several weeks before the child's death, the boyfriend had begun to force the child to put a rag in his mouth when he was beaten so that he would not cry out. A few minutes before the child was found unconscious, the boyfriend had requested pepper and had removed the lid from the shaker; he then had gone to the rear of the residence with the child. The boyfriend and the mother drove the child to the hospital where the child was pronounced dead approximately one half hour later. Although the mother initially denied knowledge of what had happened, she subsequently told the police what had transpired. The mother further stated that her boyfriend got frustrated with her because she did not discipline the child.

Examination of the child's clothing revealed pepper on the back of his shirt. The autopsy revealed contusions of the face. extremities, buttocks, and penis. There was an irregular recently healed scar over the lateral aspect of the child's left arm. The trachea, bronchi, and terminal bronchi were filled with pepper. The bronchial mucosa was hyperemic. There was pulmonary edema. The oropharynx contained a large amount of pepper. The esophagus was filled with pepper, and the stomach contained a small amount of pepper.

PATIENT 6 (From Pennsylvania).—This 2-year-old girl "stopped breathing" in the presence of her 45-year-old godfather. The godfather stated that he had been babysitting the child and that she and another child were playing in another room. When he went into the kitchen to get a drink, he saw her lying on the floor of the hallway. He stated that she had "gotten into pepper" once before. Pepper was noted on the hallway floor near where the child had been found, and a pepper shaker was present on the kitchen sink. The child was pronounced dead shortly after arrival at a local hospi-

Autopsy examination revealed abundant black pepper around the child's face and

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From the Blodgett Memorial Medical Center. Grand Rapids, Mich (Dr Cohle and Mr Trestrail); the Division of Forensic and Environmental Pathology, St Louis University School of Medicine and the Office of the Medical Examiner, St Louis (Dr Graham); the Office of the Deputy Chief Medical Examiner, Roanoke, Va (Dr Oxley); the Office of the Coroner, Lancaster, Pa (Dr Walp); and the Harris County Medical Examiner Office. Houston (Dr Jachimczyk).

| | | | Patients With Fatal | Pepper Aspira | ition | |
|------------------------|-----------------------------------|---|--|----------------------------------|--|---|
| Patient/ Age, y/Sex | Person Administering Pepper | Initial History | Reason for Incident | Evidence of Previous Abuse | Autopsy Findings | Criminal Charge/ Penalty |
| 31/2 | Mother | Mother admitted pouring pepper down child's throat | Punishment for taking bottle from infant sibling | Yes | Trachea, main-stem, and secondary bronchi filled with pepper; pepper in pharynx, 0.35 g of pepper in stomach | Guilty of manslaughter |
| 2/5/M | Foster mother | Mother admitted giving pepper | Punishment for lying | No | Pepper impacted in main- stem bronchi and within esophagus, stomach, duodenum, and jejunum; 4 mL in airway, 6 mL in Gi* tract, and 0.5 mL removed before death | Coroner's jury ruled mother's action "negligent but lawful" |
| 3/21%/F | Mother | Mother admitted pouring pepper down child's throat | Punishment for taking sibling's bottle | Yes | Pepper occluding trachea to secondary bronchi, pepper packed in stomach and first part of duodenum | Second-degree murder/20 y |
| 4/5 mo/M | Mother | Child got into pepper shaker left on floor | Punishment for putting fingers in mouth | No | Pepper impacted in infraglottic larynx, main- stem bronchi, and occasionally in distal bronchi (12 mL of pepper) | Involuntary manslaughter/ 5 y |
| 5/21/s/M | Mother's boyfriend | Child poured pepper into own mouth | Punishment for unknown offense | Yes | Pepper on clothing, pepper extending from larynx to terminal bronchi, mucosa was hyperemic | Boyfriend: injury to a child/50 y; mother: injur to a child/5 y |
| 6/2/F | Godfather | Found unconscious | Punishment for eating pepper | No | Distal trachea and proximal bronchi filled with pepper (3-5 mL), 3 mL of pepper in esophagus, and pepper in stomach | Charged with general homicide, acquitted in jury trial |
| 7/10/M | Adult male friend | Found unresponsive in bathtub | Punishment for not eating breakfast | Yes | Larynx, trachea, and large and small bronchi covered by pepper mixed with Worcestershire sauce; pepper in oropharynx, esophagus, and stomach | Charged with murder |
| 8/4/M | Self | Child ingested pepper | Pica | No | Nonocclusive pepper in trachea, larynx, and stomach; pneumonia with diffuse alveolar damage; organic brain disease | None: self- administration, accident |

^{*}GI indicates gastrointestinal.

palm of each hand. An endotracheal tube in the mouth contained a small amount of black pepper. Faint contusions were noted on the buccal surfaces of the upper and lower lips.

Examination of the airway revealed that the distal trachea and proximal bronchi were filled with an estimated 3 to 5 mL of pepper. There was bilateral pulmonary edema. Approximately 3 mL of pepper was present in the esophagus, and pepper was also noted to be in the stomach. The godfather subsequently confessed that the child had been eating pepper, and he poured pepper into her mouth to "teach her a lesson." The lid from the shaker had been removed by the child.

PATIENT 7 (From New Jersey).—This 10-year-old boy was living for the summer with a man and his wife; the husband had been the child's "Big Brother." The assailant (the adult male) initially stated that he heard a noise that sounded like a fall coming from the bathroom, and when he broke through the door, he found the child unresponsive in the bathtub, which contained water. He stated that he removed the child from the bathtub and called for assistance. It was noted by the first responders that the child's hair and underpants were dry. He was taken to an emergency department where a gastric lavage revealed what appeared to be bloody fluid and material consistent with black pepper. When confronted with this, the assailant admitted that he had forced the child to ingest pepper as punishment for not eating breakfast.

According to the wife, the assailant forced the child to ingest pepper and Worcestershire sauce after he had thrown the child to the floor, placed his knees on his upper abdomen, pinched his nose, and forced the pepper and Worcestershire sauce into his mouth. He then banged the child's head on the back of a wooden chair and took the child into the bathroom. Approximately ten minutes later, the assailant called for medical help.

Additional history indicated that on previous occasions the assailant had forced the child to ingest pepper and occasionally Tabasco sauce or horseradish; he would then take the child into the bathroom and hold his head in the toilet. On previous occasions, the child had stated that he had been beaten by the assailant, and the assailant himself admitted having slapped the child on numerous occasions.

The autopsy revealed a laceration of the deceased child's lower lip, a recently healed abrasion of the right temple and cheek, and several contusions of the left side of the chest. There were numerous small contusions on the medial aspect of the right arm, three of which were consistent with having been made by a finger. There was a contusion on the left shoulder, a laceration of the left leg, and a laceration of the left thigh. The larynx, trachea, and bronchi, including the smallest visible bronchi, contained large amounts of pepper. An odor suggestive of Worcestershire sauce was noted. Pepper was present in the esophagus and stomach. There were three serosal contusions within the duodenum.

COMMENT

Common black pepper is the unripe dried fruit of the woody perennial plant, *Piper nigrum* (family, Piperaceae). Black pepper contains 2% to 4% volatile oils that consist of a complex mixture of monoterpenes (70% to 80%) and sesquiterpenes (20% to 30%), 5% to 9% piperine (trans,trans-5,3 [4-methylenedioxyphenyl-2, 4-pentadienoic perididel]), piperidine, piperettine, chavicin, and other minor alkaloids.⁴

Piperine, the primary irritant in pepper, is usually initially tasteless but produces a burning aftertaste. It is neutral to litmus, and practically insoluble in water (40 mg/L). It has been used as an insecticide because it has a toxicity to houseflies greater than that of pyrethrum. Contact with ground pepper can cause redness of the eyes and swelling of the eyelids.

It is clear that the seven cases of homicidal pepper aspiration have much in common with other, more typical types of child abuse. Each victim was a young child—all but one were 5 years of age or younger, and consequently much smaller than the adult assailants. In each instance, the reason for the pepper administration was punishment. The perpetrators were all caretakers of the children, and they included the mother (three patients), foster mother, godfather, mother's boyfriend, and an adult male friend (one patient each).

For four patients, the assailant initially gave an incorrect history as to how the child was asphyxiated. For patient 2, the foster mother stated that her intent was to punish the child by shaking a few grains of pepper onto his tongue: yet, she removed the entire lid of the shaker to do this. The top of the plastic pepper container had perforations capable of discharging small amounts of pepper. In four instances, the child had been abused before. In the lone accidental deaths (patient 8, Table), there was a history of pica and emotional upset within the family. The autopsy documented the presence of organic brain disease and the absence of acute and chronic abuse.

Mechanical obstruction and mucosal edema are the two mechanisms of death. For patients 1 through 7, whose deaths were certified as homicides, the mechanism of death was mechanical obstruction of the airway. Sheahan and others⁸ postulated that the child in their report asphyxiated by a combination of airway obstruction and piperine-induced mucosal edema. In the nearly fatal case of pepper aspiration described by Flintoff and Poushter,7 a 2½-month-old female infant poured an unknown quantity of pepper into her mouth. She presented with dyspnea 30 minutes later that required a tracheostomy with ventilatory assistance, tracheobronchial lavage, and steroid administration. She was discharged in good health two days later. In this patient, the airway obstruction was ascribed solely to mucous membrane swelling caused by the irritant effects of pepper.

Failure to recognize the criminal nature of the act may result in no punishment. In patient 2, despite the fact that the crime fit the criteria for involuntary manslaughter, namely, gross negligence on the part of the foster mother, a coroner's jury found her conduct to be "negligent but lawful," and she was not prosecuted. In patient 6, the defendant was acquitted in a jury trial. Sentences for those persons who were convicted ranged from five to 50 years.

Black pepper exposures that were reported to two regional poison centers were reviewed. These cases were reported by parents, other caretakers, or the victims themselves to the poison

centers, seeking advice on treatment. At the Blodgett Regional Poison Center in Grand Rapids, Mich, from January 1985 to March 1987, there were 20 black pepper exposures out of 68 036 total cases for a prevalence of 2.8/10 000. Of these 20 cases, 15 were ocular, two were ingestion only, and one each were ingestion and ocular, ingestion and dermal, and dermal. One of the ingestion cases was a probable food allergy in a 26-year-old woman, and the others occurred in children aged 1 to 2 years who were found eating pepper. One 2-year-old child exhibited sneezing and crying, along with redness of the exposed eye. In no case did the poison specialist have to refer the child for medical care. The National Capital Poison Center in Washington, DC, had eight cases of black pepper exposure out of 52013 in 1985 and 1986, for a prevalence of 1.5/10000. Seven cases were ocular and showed symptoms of eye irritation. The lone case of ingestion occurred in a 3-year-old child who dumped a box of pepper in his mouth and subsequently vomited. mother washed his mouth with water and, on a follow-up call on the next day, reported that he was well. All exposures were apparently accidental. With the exception of the food allergy, all ingestions involved only the gastrointestinal tract. None of these required medical treatment. Nationally, there were 391 cases of black pepper exposure in 1985 and 1986. During this time, 1999 407 calls were received for a prevalence of 2.0/10000.

It is clear that nearly all cases of pepper aspiration are a manifestation of child abuse. The lone accidental death in this series was documented by obtaining the medical history, scene investigation, and autopsy, all of which should be performed in every sudden unexpected death of a child. The report of the nonfatal case of purportedly self-administered pepper aspiration by Flintoff and Poushter' does not mention whether forced administration of pepper was excluded. We recommend the following to physicians who encounter children who have aspirated pepper: (1) obtain a thorough history, including the circumstances under which the injury took place, examine the offending pepper container and the scene when appropriate, and obtain the medical history with child abuse reference; (2) perform a thorough physical examination/autopsy with estimation of the amount of pepper ingested, examination of the buccal mucosa, and notation of any recent or remote injuries; and (3) when warranted, contact a child protective

service worker and local police agency. The wide geographic distribution of these deaths suggests that the administration of pepper as a form of punishment is not restricted to any particular locale. The fact that most cases have occurred in the last two years suggests that this form of abuse is increasing in frequency.

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Neurofibromatosis: Conference Statement

National Institutes of Health Consensus Development Conference (Arch Neurol 1988;45:575-578)

ARCHIVES OF SURGERY

The Scalp as a Donor Site in Burns

Edmond A. Zingaro, MD; Angelo Capozzi, MD; Vincent R. Pennisi, MD (Arch Surg 1988;123:652-655)

Intentional Ipecac Poisoning in Children

H. Juhling McClung, MD; Robert Murray, MD; Nancy Jo Braden, MD; John Fyda, MD; Robert P. Myers, DO; Lynn Gutches, ACSW

• Ipecac (emetine) is a safe emetic for emergency home use. Its ready availability also provides the potential for child abuse and chronic self-induced emesis. The chronic administration of ipecac can result in unusual symptom complexes such as chronic diarrhea and vomiting, muscle weakness, colitis, cardiomyopathy, fever, edema, or electrolyte disturbances. We describe patients who were intentionally poisoned and who demonstrated these symptoms. Because of the widespread use of ipecac for therapy in acute accidental polsonings, toxicology laboratories may not look for or report the presence of this drug in their routine screens. This may delay the recognition of chronic ipecac poisoning in patients. (AJDC 1988;142:637-639)

In an effort to curtail complications from accidental poisoning in children, the use of syrup of ipecac has been widely advocated. Although it has been accepted as a safe drug for inducing emesis, toxicity from chronic ingestion of this drug has been described in both the lay and medical literature, especially in patients with anorexia nervosa.2,3 We recently treated three patients with chronic poisoning by parental administration of ipecac. These three children shared common features of presentation, parental behavior, and hospital course.

PATIENT REPORTS

PATIENT 1 .- A 10-month-old female infant was referred for recurrent diarrhea and vomiting. She had previously been

admitted on multiple occasions to both local and referral hospitals with negative evaluations and persistent symptoms. She was well nourished and had a mild delay in motor function. Her liquid stools were repeatedly normal on culture, and results of examinations for ova and parasites were normal. No white blood cells, red blood cells, or significant volumes of stool were detected. The level of α_1 -antitrypsin in her stool, a measure of protein loss, was mildly elevated. Results of a jejunal biopsy were normal. Colonoscopy showed streaks of erythema, and a biopsy specimen indicated mild colitis. The child responded to the gradual introduction of soy formula and was discharged; she was readmitted within two days for vomiting. Diarrhea was less prominent. Sporadic emesis continued despite the withdrawal of feeding. Although the child could not tolerate ice chips, results of an upper gastrointestinal tract barium swallow and a nuclear gastric emptying study were normal. Results of multiple toxicology screens of the urine were normal. The child became progressively more irritable and weak as repeated attempts to advance feedings failed, so parenteral nutrition was initiated. A chest effusion of obscure cause developed, which required thoracentesis.

During the course of the hospitalization, the mother became alternatively frantic and accusatory. She frequently refused to allow tests to be performed and threatened to take the child to another institution. Another parent on the floor reported that this mother had bottles of ipecac in her purse. Screening tests for ipecac were positive on multiple samples using control standards and two separate analytical methods. All symptoms resolved rapidly once the child was separated from her mother. Only after the diagnosis was established did the maternal grandparents confess concern about previous maternal behavior and competence.

This patient was discharged to a foster home in the temporary custody of children's services. She remained there for approximately 18 months. The child was returned to the home only after this young single mother, who initially refused to comply

court-ordered recommendations, completed a psychological evaluation, psychiatric counseling, and parenting classes. The protective services agency has remained involved with the family after 21/2

PATIENT 2. - A 21-month-old male infant was admitted with a complicated history of vomiting and diarrhea and multiple hospitalizations. According to the mother, the patient had begun episodes of vomiting shortly after birth and was hospitalized for dehydration at 3 weeks of age. All test results were normal. At the time of admission, the mother reported between ten and 15 episodes of vomiting per day associated with occasional diarrhea. His height and weight were approximately the 95th percentile for age. Results of the physical examination were unremarkable. Although results of serum, stool, and radiologic studies were normal, the child continued to vomit. Because of inconsistencies between the history and physical findings, toxicology screens of vomitus and urine were requested. All test results were negative until we requested evaluation for ipecac (Toxi-Lab TLC screen, Marian Scientific. Kansas City, Mo), which was detected in both urine and vomitus. The mother's visitations were restricted, and the child was given a regular diet and had no further symptoms. It was then discovered that this child was the object of a custody battle. which may have provided a motivation for the poisoning.

At hospital discharge, the natural father and his wife were given temporary custody. The mother completed parenting classes as advised by children's services. She did not, however, complete the recommended counseling sessions. Primarily due to the father's agreement, the child was returned to the home of his mother and her husband after 11 months. Children's services has remained peripherally involved after 22 months.

PATIENT 3. - Admission of this 8-monthold boy was prompted by the mother's appeal for help after local physicians had failed to diagnose the cause of his chronic vomiting and diarrhea. The child had been hospitalized for these symptoms at 1, 3, 6.

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Chronic Toxicity of Ipecac

Gastrointestinal symptoms
Nausea
Vomiting
Diarrhea
Esophageal stenosis
Hemorrhage
Mucosal irritation
Neurologic symptoms
Prolonged weakness
Peripheral neuritis

Convulsions

Cardiovascular symptoms
Tachycardia
Arrhythmias
Cardiomyopathy
Shock
Miscellaneous symptoms
Weight loss
Edema
Electrolyte imbalance
Allergic reactions
Fever
Macular rashes

and 8 months of age, and each episode had resolved without a diagnosis. He was well nourished but appeared "floppy" and had a six-month developmental delay. His stools became well formed within the first few days, and results of an extensive evaluation were negative. His muscle tone and motor skills improved, and he was discharged receiving regular formula. Several days later, diarrhea resumed, along with the symptom of progressive "floppiness" and a macular rash. Striking truncal weakness associated with asymmetric weakness in the limbs was noted, although the peripheral reflexes were intact. During this evaluation, diarrhea and vomiting became increasingly prominent but occurred with no relation to meals or time of day. His weight was maintained. Results of an upper gastrointestinal tract series with a smallbowel follow-through, electroencephalogram, and computed tomographic scan were normal, as were muscle enzyme lev-

The child was relatively content and consumed an adequate intake of formula, but the tearful mother frequently challenged the physician's lack of a diagnosis and demanded "that something be done." Because the vomiting did not fit anticipated patterns, a urine screen was done for ipecac, and results were positive. Bottles of ipecac were found in the patient's closet. The mother admitted that she felt the need to maintain the physicians' interest in her child's case. On separation, vomiting abated. The muscle weakness resolved over several months.

Children's services received temporary custody of this child and his 4½-year-old sister for three months during foster home placement and then received a protective service order that covered approximately the next 16 months. The mother did complete the required ten counseling sessions and family life classes. The protective agency personnel currently have concerns over inappropriate and repeated complaints about illnesses in the child that have not been substantiated by the local physician. There is a homemaker in the family

home one day each week for support, but the situation appears unresolved.

COMMENT

Ipecac has achieved broad public awareness. It has been promoted as a safe emetic, has been endorsed for use in poison control kits, and is disseminated widely to households with children. The acute and chronic toxicities of this drug, however, have not been emphasized to physicians.

Ipecac is a natural product composed of emetine, cephaeline, and psychotrine. Emetine has the most pharmacologic activity to produce nausea, vomiting, and diarrhea. It has been used since 1912 as an amebicide. This long-term use led to the description of its chronic effects.

Emetine persists in body organs up to 60 days after systemic treatment. Ordinarily, the gastrointestinal effects dramatically reduce systemic absorption; however, emesis can be delayed or incomplete in the presence of milk or subemetic doses of ipecac.8 Toxicity after systemic absorption of emetine is cumulative and has prominent effects on the gastrointestinal, neuromuscular, and cardiovascular systems9-18 (Table). The cardiac manifestations are the most dangerous. They include initial tachycardia followed by flattened and inverted T waves and a prolonged QT interval on the electrocardiogram, which can be associated with fulminant cardiomyopathy and death from cardiac failure.11 These three patients illustrate the gastrointestinal, cutaneous, and neuromuscular symptoms⁹⁻¹⁴ (Table). The chronic symptoms can last for weeks, since more than one third of the drug is retained in the body longer than 35 days.7 While acute hemorrhagic enteropathy is a complication of acute overdose, it is not a feature of chronic toxicity.¹⁵

Although the presenting complaints were vomiting and diarrhea, the patients share common features of intentional poisoning.16 Parents referred the children and voiced their frustration with the persistence of symptoms in spite of multiple negative evaluations at other hospitals. The children, all less than 2 years of age, appeared well nourished. In two cases, development appeared delayed because of poor gross motor control. The pattern of vomiting and the tempo of its course were not typical for infectious, anatomic, or metabolic causes. Tolerance of feeding was sporadic, but barium radiologic and nuclear gastric emptying studies were tolerated, and results were normal in each patient.

All three children were poisoned by their natural mothers, who seemed oblivious of the danger to their children from their actions. This conforms to the disorder recently labeled as "Munchausen's by proxy."17 The three mothers verbalized their concern as the child's medical status deteriorated and uncomfortable therapeutic and diagnostic maneuvers were undertaken; however, the episodes of emesis increased over the course of hospitalization. Symptoms immediately subsided after separation from the mother. A history of social disruption had been carefully concealed, and the hospitalization had obviously supplied each mother with substantial personal gain.

Initial urine screens did not detect ipecac, because many standard laboratory procedures do not include it. We recommended that toxicology laboratories utilize methods that include ipecac in their screens and report its presence in all samples and that physicians who suspect chronic vomiting from factitious causes request urine screening specifically for ipecac. In spite of the importance of ipecac in the management of acute accidental ingestions, ^{18,19} physicians should be aware that the drug has a potential for both acute and chronic abuse.

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JAMA

'Doctors Must Not Kill'

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Debbie's Dying: Mercy Killing and the Good Death

K. L. Vaux (JAMA 1988;259:2140-2141)

'It's Over, Debbie' and the Euthanasia Debate

G. D. Lundberg, MD (JAMA 1988;259:2142-2143)

The Emergence of Grade A Eggs as a Major Source of Salmonella enteritidis Infections

M. E. St Louis; D. L. Morse; M. E. Potter; T. M. DeMelfi; J. J. Guzewich; R. V. Tauxe; P. A. Blake; the Salmonella enteritidis Working Group (JAMA 1988;259:2103-2107)

Syrup of Ipecac

The Case for Distribution From Physicians' Offices

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 Data from a nationally representative sample of household interviews were analyzed to examine public preparedness for childhood poisoning episodes. Eighty-eight percent (61% to 77% in nonwhite groups) of respondents from households with children younger than 10 years had heard of poison control centers and 70% (50% to 57% in nonwhites) stated that they had the telephone number of such a center. In contrast only 25% stated they had syrup of ipecac in their home. Among blacks and Hispanics this proportion was 9%. To explore possible reasons for this we telephoned a sample of 65 physicians listed in the greater Washington, DC. telephone directory as providers of care for infants and children. Of the 45 (69%) who agreed to be interviewed, 73% informed their patients about poison controi centers and 53% provided the appropriate telephone number. Although 78% believed parents should have ipecac in the house, only three (7%) of 45 actually dispensed ipecac to parents. We conclude that ipecac is not widely available in the homes of American children. By regularly dispensing it in the course of pediatric care, physicians could largely remedy this deficiency.

(AJDC 1988;142:640-642)

Despite the continued drop in deaths attributable to childhood poisoning,¹ the ingestion of toxic substances by children continues to be a significant public health issue.^{2,3} As many as 130 000 children under 5 years of age were estimated to ingest poisons in 1986.¹ The introduction of safety caps and public education about accidental ingestions and about appropriate

steps in case of ingestion have been the key public health approaches to this problem. In this communication we examine the impact of the educational effort on various segments of the US population.

For editorial comment see pp 595 and 596.

Using the 1985 Health Promotion and Disease Prevention Supplement of the National Health Interview Survey (NHIS), we estimated by several demographic characteristics the proportion of the US population with children under 10 years of age that had heard of a poison control center, that had the telephone number of a poison control center, and that had syrup of ipecac in the home. We also conducted a small telephone survey of pediatricians in the Washington, DC, area to ascertain their attitudes and practices with respect to poison prevention. **METHODS**

The NHIS is a continuous survey conducted by the National Center for Health Statistics that obtains basic information on the health knowledge, behavior, and practices of the US population. This survey is a complex multistage area probability sample. Basic health and demographic information is obtained from a weekly national probability sample of US households. A random subsample is selected to respond to questions of special interest. The NHIS of 1985 consisted of 36399 eligible households. The questionnaire administered to the sample consisted of two parts. The first part requested information on basic health, socioeconomic variables, and demographic variables. The second part requested information on accident/disease prevention and health promotion behavior. The nonresponse rate for the Health Promotion and Disease Prevention Questionnaire was approximately 11%. Details of the 1985 Survey have been previously published.4

The questions pertaining to childhood poisoning on the 1985 supplement were as follows: (1) Have you ever heard about poison control centers? (2) Do you have the telephone number for a poison control center? (3) There is a medication called ipecac syrup that is sometimes taken to cause vomiting after something poisonous is swallowed. Do you now have any ipecac syrup in this household?

Responses to these questions from households with children less than 10 years of age were cross tabulated by the age of the household informant, ethnicity, marital status, the highest educational level achieved by the responsible adult family member, family income, and location in a metropolitan statistical area. Results are presented as the proportion of the US population responding positively to these questions. This estimate was derived from weighted responses of the households in the survey.

Sixty-five physicians listed in the Washington, DC, telephone directory as providing care to infants and children were randomly selected for a telephone interview. The interview consisted of ten questions concerning preventive health measures that these physicians may or may not have incorporated into their practice. Forty-five (69%) physicians agreed to be interviewed.

RESULTS

Overall, 88% of respondents had heard of poison control centers. These proportions varied by age of the respondent, ethnicity, educational status, income, and locale (Table). For example, 94% of whites responding had heard of poison control centers, while only 61% of "other" races (excluding blacks and Hispanics) had heard of such centers. Educational status also affected the response to this question. Only 69% of households where the highest level of education

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Response to Questions Concerning Poison Prevention Behavior From the 1985 Health Promotion Disease Prevention Supplement of the Health Interview Survey

| | Have Heard of Polson Control Centers, % | Have Telephone Number of Center, % | Have Ipecac in Household, % |
|-------------------------------|---|--|--------------------------------|
| Overall | 88.1 | 69.9 | 25.4 |
| Age of respondent, y | | | |
| 17-24 | 82.2 | 55.3 | 11.6 |
| 25-34 | 91.1 | 73.5 | 28.3 |
| 35-44 | 90.5 | 73.3 | 31.5 |
| ≥45 | 75.3 | 62.1 | 14.8 |
| Ethnicity White | 94.1 | 74.5 | 30.8 |
| Black | 77.4 | 54.8 | 8.8 |
| Hispanic | 66.9 | 56.9 | 9.0 |
| Other | 61.2 | 50.0 | 15.1 |
| Educational status, y 0-11 | 69.2 | 51.0 | 7.0 |
| 12 | 88.2 | 66.3 | 18.8 |
| 13-15 | 91.7 | 72.0 | 27.3 |
| 16 | 92.6 | 77.0 | 36.8 |
| ≥17 | 93.8 | 81.5 | 45.4 |
| Local* MSA, central city | 83.3 | 07.7 | |
| MSA, noncity | 90.1 | 67.7 | 21.3 |
| Non-MSA | 90.1 | 74.4 | 56.5 |
| Annual family income, \$ | 90.2 | 63.7 | 19.1 |
| <5000 | 77.3 | 56.9 | 9.8 |
| 5000-6999 | 82.3 | 59.3 | 11.7 |
| 7000-9999 | 76.7 | 54.7 | 11.6 |
| 10 000-14 999 | 83.9 | 59.3 | 15.3 |
| 15 000-19 999 | 85.4 | 65.3 | 21.9 |
| 20 000-24 999 | 91.5 | 70.6 | 25.7 |
| 25 000-34 999 | 91.7 | 75.7 | 28.4 |
| 35 000-49 999 | 93.6 | 76.0 | 35.9 |
| ≥50 000 | 93.9 | 78.0 | 40.9 |

^{*}MSA indicates metropolitan statistical area.

was 11 years or less responded positively to this question compared with 94% for households with a member who had 17 or more years of education.

About 70% of respondents from households with children less than 10 years old indicated that they actually had the telephone number of a poison control center. Educational status was associated with substantial variation in this proportion. Only 51% of respondents with 11 years of education or less had the telephone number of a poison control center compared with 82% of those with 17 years or more of education. Differences in ethnicity. age, and family income also accounted for 20% to 30% variation in the proportion of households having this information.

In contrast to the widespread

knowledge of poison control centers was the limited proportion of homes with children under 10 years of age in which ipecac was available. This amounted to only 25% overall. It was 9% for black and Hispanic households and 7% for households in which the respondent had not completed 12 years of school. Ipecac was most likely to be present in suburban homes where 56% reported having it on hand. Among homes with children under 5 years of age, the overall proportion having ipecac was 26% (not shown).

To explore physician practices in poisoning prevention we attempted telephone interviews with 65 practitioners who had listed themselves in the metropolitan Washington, DC, "yellow pages" under "Pediatrics." Of the 45 (69%) we were able to interview.

33 (73%) informed parents of the existence of poison control centers and 24 (53%) supplied a center telephone number. While more than three quarters (35 [78%]) of these physicians told parents to keep ipecac at home, only three (7%) (95% confidence interval = 1% to 18%) actually dispensed it from their offices.

COMMENT

In the 1950s, accidental ingestions of toxic substances were estimated to occur in some 500 000 children a year and caused 500 deaths annually.5 The first Poison Control Center, which was organized in response to this problem, opened in Chicago in 1953. Since that time several national organizations have evolved to help coordinate the exchange of diagnostic and therapeutic information. Congress has mandated safety packaging standards for drugs and other toxic substances and in 1962 established an annual National Poison Prevention Week to heighten the public's awareness of the problems associated with childhood ingestions. Since that time poison-related deaths in children less than 5 years of age have decreased from 450 in 1961 to 55 in 1983.1

The 1985 Health Interview Supplement provides substantial evidence of the success of this educational effort. Nine of ten respondents with young children had heard of poison control centers and seven of ten said they had a telephone number available. However, ipecac was available in only one quarter of these households, and in rural areas, where delays in getting medical assistance are especially a problem, the proportion with ipecac was even lower.

In a society where accurate poison control information is as close as the nearest telephone it is logical that the parents of small children should be equipped to act quickly when an emetic is needed. Despite limited dissent, there is a considerable consensus in the medical and public health communities on the safety and value of ipecac for this purpose. An extensive study of its safety was recently reported. It is recommended by the American Academy of Pediatrics as well as the American Association of

Poison Control Centers and has been judged by the Food and Drug Administration to be safe enough to make available without prescription. In our small survey, 78% (35/45) of physicians caring for young children recommended that parents keep it at home.

It is clear that despite this consensus most homes with young children do not have ipecac available. Although we are hesitant to generalize, the limited survey we conducted in metropolitan Washington, DC, strongly suggests a discrepancy between advice and action in the medical community. We believe that physicians and

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When ipecac is dispensed from an office or clinic, the drug should be appropriately labeled with the telephone number of the nearest poison control center, instructions to call the

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center before using ipecac, and the usual list of contraindications. The process of handing the ipecac to parents would create an additional opportunity for the physician or his staff to discuss accident prevention directly with parents. Obviously, where communication across language barriers or parental competence is in serious question, the drug could be omitted. By incorporating the distribution of ipecac directly into pediatric care, it should be possible to place it in the homes and consciousness of most American parents in a relatively few years.

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In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY-HEAD & NECK SURGERY Surgical Dimensions of the Facial Recess in Adults and Children

Steven A. Bielamowicz, MD; Newton J. Coker, MD; Herman A. Jenkins, MD; Makoto Igarashi, MD (Arch Otolaryngol Head Neck Surg 1988;114:534-537)

Epidemiology of Human Bites to Children in a Day-care Center

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• The purpose of this study was to examine the epidemiology of human bites to children in a day-care center over a one-year period. This was a cohort study based on the injury log maintained on a daily basis by staff of the day-care center, as required by state licensure law. A total of 224 children was enrolled in the center during the study period: 29 infants (ages 0 to 16 months), 62 toddlers (16.1 to 30 months), and 133 preschoolers (30.1 to 72 months). One hundred four children were bitten one or more times by other children in the center, with a total of 347 bites. The bite rates (defined as number of bites per 100 child days of enrollment in the center) varied significantly by age group but not by gender for initial or first-time bites, with toddlers having the highest rate and preschoolers the lowest (infants, 0.7129; toddlers, 1.3672; preschoolers, 0.4193). Total bite rates (which took into account multiple bites per child over the 12month study period) varied significantly by age group, with toddlers having the

Human bites can pose a serious medical problem due to the possibility of physical trauma or infection.1 The research literature on human bites can be categorized into roughly three areas: human bites by children or adults, human bites in institutional settings, and the treatment of bites. The research literature on biting behaviors, especially by children, tends to focus on exploration of the psychological reasons for biting behaviors.2 The studies in the literature that de-

highest rate per 100 days of enrollment and preschoolers the lowest (infants. 2.1931; toddlers, 3.1300; preschoolers, 0.5611). Males and females differed significantly in total bite rates per 100 enrollment days within the toddler age group (males, 3.6683; females, 2.3096) but not within the other two age groups. None of the demographic characteristics available in this study distinguished between children who were bitten compared with those who were not bitten with the exception of number of days of enrollment. The circumstances surrounding the biting events were examined with respect to the activity of the child when bitten, the victim's location when bitten, body part bitten, and treatment by staff. The results of this study raise policy questions about treatment protocols for human bites of children in group child-care settings, the routine recording of biting events, and the ethics and practice of reporting such events to

(AJDC 1988;142:643-650)

scribe bites of children by adults are often in the context of a discussion of clinical evidence in child-abuse cases.3 or in the context of bites by adults in fights, with a distinction being made between actual bite wounds and clenched fist injuries.4 There are also descriptions of biting incidents in institutional settings,5 especially among mentally retarded6 children or adults. The third major body of literature on bites concentrates on clinical manifestations and medical or surgical treatment of bites,7 especially of the hand.8 One epidemiologic study of 892 human bites has been reported in the literature during the past two decades based on physician reports to the New York City Department of Health in which rates were given for different age groups ranging from infants through adults.9

To our knowledge, no studies have

been reported in the literature of the rates of human bites of noninstitutionalized preschool children in nursery school or day-care settings in the United States. With an increase in the number of young children being placed in such group child-care settings due to entrance by both parents or single heads of households into the labor force, 10 questions arise about the extent to which human bites occur to children in these settings.

The intent of this study was to conduct an initial inquiry into the epidemiology of human bites of children by other children in a day-care center. Specifically, three major research questions were addressed: (1) What were the rates of human bites? (2) How did children who received human bites in a day-care center differ from those who did not in terms of age group, gender, month of enrollment in the day-care center during the study year, and number of days enrolled in the daycare center? (3) What were the circumstances surrounding the biting incidents in terms of the injury events and their consequences?

METHODS Day-care Center

This was a cohort study based on the injury log of one day-care center for the calendar year of 1984. Data were abstracted from the injury log by the study team at the end of 1984. The facilities of the center were located in a suburban area in a free-standing building consisting of three large rooms, plus a kitchen, bathroom facilities for children and adults, an office for the center director, and a staff lounge. The center, licensed by the state for group child care, is a private, for-profit organization that is part of a national chain. Children were enrolled for part-time and full-time day-care between 7 AM and 6 PM, Mondays through Fridays, with no service provided on national holidays. The children were

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assigned to one of three age groups: infants (aged 0 to 16 months), toddlers (16.1 to 30 months), and preschoolers (30.1 to 72 months). These age groupings were defined by state licensure law that required different staff-to-child ratios: 1:4 for infants, 1:7 for toddlers, and 1:10 for preschoolers. Cost per day of child care by the center also varied inversely by age group, with daycare for preschoolers costing the least. Separate rooms were provided for each of the three age groups, and the staff of the center moved a child from one room to another when the child transitioned from one age group to another, eg, at age 16.1 months a child was moved from the infant to the toddler room.

Instruments

Three sources of data were used in this study: an injury log, a biographical information form about each child completed by the parent at time of admission to the center, and financial records of the center that were used to document the child's enrollment in the center during the study year. State licensure law requires that all day-care centers maintain a daily injury log consisting of a written summary of any injury sustained by a child being cared for in the center. The injury log must be completed by a staff member at the time the injury occurs and must include the name of the child, a brief description of the injury, and the type of treatment provided.

A comprehensive coding protocol does not exist in the research literature for the coding of nonfatal injuries to children; therefore, several existing standardized coding systems were used, including the International Classification of Diseases, Ninth Revision, N-codes used for type of injury and International Classification of Diseases, Ninth Revision, E-codes for source and cause of injury, 11 the National Electronic Injury Surveillance System 12 for the product involved in the injury, and the Supplementary Data System 13 for the part of the body.

Subjects

A total of 224 children enrolled in the day-care center during the study year: 29 infants (20 males; nine females), 62 toddlers (35 males; 27 females), and 133 preschoolers (70 males; 63 females). The children were from predominantly white, middle-class families living in the surrounding suburban area. A child was defined as a subject for this study if he or she was enrolled one or more days or portion of a day in the day-care center, as documented by the financial records of the center. Subjects with human bites were those reported in writing by staff in the center's injury log as having

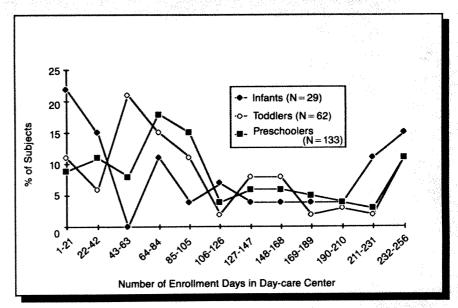


Fig 1.—Percent of subjects within each age group by enrollment days by age group.

received such an injury at the day-care center. Subjects without human bites were those children enrolled in the center but whose names did not appear on the injury log as having been bitten while at the day-care center, although they could have been reported as having received some other kind of injury.

Statistical Procedures

Calculation of Rates.-The standard definition of a rate was used in this study: the number of events (human bites) divided by the total number of children at risk. A child was not at risk if he or she was not in attendance at the day-care center, and because of the wide variation in number of days of enrollment in the center, as shown in Fig 1, it was necessary to compute these rates on the basis of child days of enrollment rather than the number of children. The information in Fig 1 takes into account the possibility that a child could be a fulltime enrollee, ie, eight hours a day, five days a week, 52 weeks a year, or a part-time enrollee, with enrollment consisting of a few hours two days a week or only mornings every day of the week, or only part time from September to May, then full time from June to August, etc. Also, because of the physical separation of the children by age groups, a subject in this study might contribute some of his or her enrollment days to two age groups. For example, a child who entered the center as a toddler and became a preschooler during the study year contributed a proportionate number of enrollment days to each of these age groups, and the number of days was calculated exactly based on date of initial enrollment, the child's birthdate, and the financial records of the center (as a surrogate for attendance records). The same child who received a human bite as a toddler but not as a preschooler would contribute to the numerator of the rate in the former but not in the latter age group.

For purposes of this study, one day of enrollment was equal to an eight-hour day; fractions of a day were included in these calculations. For the calender year of 1984, a total of 256 enrollment days was possible. The information available in this study was limited to the number of hours per day and the number of days per week a parent had paid for the child for each week; thus, detailed rates of human bites by specific day of the week (eg, Mondays or Tuesdays) or by a specific hour of the day were not possible.

Initial and Total Bite Rates.-Two kinds of rates per 100 child days of enrollment are described in this report: (1) an initial bite rate and (2) a total bite rate. An initial bite was the first bite a child received during the study year, and the initial bite rate was therefore defined as the number of initial bites divided by the total number of children at risk for receiving a bite injury, adjusted for exposure to such an injury. In general, the denominator for the initial as well as the total bite rate was based on number of days each child was enrolled in the day-care center. (Both of these rates, initial and total, were multiplied by 100 for ease in discussing number of bites per 100 days of enrollment in the day-care center.) In calculating the denominator for the initial bite rate, the following rationale was used: each child was at risk for an initial bite each day he or she was enrolled in the day-care center during

| | | Infant | | | Toddler | | F | reschoole | r | | Total | |
|---|--------|--------|--------|--------|---------|--------|--------|-----------|--------|--------|--------|--------|
| | M | F | Total | M | F | Total | M | F | Total | M | F | Total |
| No. of children enrolled | 20 | 9 | 29 | 35 | 27 | 62 | 70 | 63 | 133 | 125 | 99 | 224 |
| No. of initial bites | 8 | 7 | 15 | 24 | 19 | 43 | 28 | 18 | 46 | 60 | 44 | 104 |
| No. of child days enrollment to initial bite | 1406 | 698 | 2104 | 1997 | 1148 | 3145 | 5513 | 5457 | 10 970 | 8916 | 7303 | 16 219 |
| Initial bite rate per 100 child days | 0.5690 | 1.0029 | 0.7129 | 1.2018 | 1.6551 | 1.3672 | 0.5079 | 0.3299 | 0.4193 | 0.6729 | 0.6025 | 0.6412 |

the study year until that point in time when he or she was bitten the first time, then the bitten child was no longer at risk for an initial bite; therefore, the remaining enrollment days following the initial biting event for that child were not included in the denominator of this rate. A child who did not receive a human bite during the study year continued to be at risk for the entire year of the study; thus, all of his or her enrollment days throughout the study year were included in the denominator in the calculation of the initial bite rate. In summary, the denominator for the initial bite rate consisted of the sum of the enrollment days up to the initial bite for the child who was bitten plus all of the enrollment days throughout the study year for the child who was not bitten.

The total bite rate was the total number of bites reported during the study year divided by the total number of child days of enrollment for bitten and nonbitten subjects multiplied by 100. In other words, a child was at risk for a human bite every day he or she attended the day-care center. whether he or she had received a bite previously or not. A distinction between initial and total bite rates was necessary because of the potential of multiple bites per child, which were defined as two or more separate biting events that occurred at separate points in time and were recorded as separate events in the injury log for the same individual. A single biting incident that resulted in physical insult to two or more body parts of the same individual was not considered a multiple bite.

Statistical Assumption.—It was necessary to assume that each biting event was an independent event to use inferential statistics in analyzing data on total bites. This assumption refers to the biting events and not to who was bitten. It assumes that a human bite in a day-care center has the same probability of happening on each day the center is open throughout the study year. In addition, this assumption of the independence of injury events has gained conceptual support in the research literature on injuries in other settings, par-

| | Rate per Child Day Used to Compute Expected Values | χ² | df | p |
|-----------------------------------|--|----------|----|-----|
| Ital bites | | | | |
| Gender within age group Infant | 0.0071 | 0.7014 | 1 | NS |
| Toddler | 0.0137 | 0.7874 | 1 | NS |
| Preschooler | 0.0042 | 0.8522 | 1 | NS |
| Age group within gender M | 0.0067 | 10.8060 | 2 | .01 |
| F | 0.0060 | 29.8236 | 2 | .00 |
| ital blies | | | | |
| Gender within age group Infant | 0.0219 | 1.6012 | 1 | NS |
| Toddler | 0.0313 | 8.3610 | 1 | .01 |
| Preschooler | 0.0056 | 3.3207 | 1 | NS |
| Age group within gender | | | | |
| M | 0.0181 | 128.8725 | 2 | .00 |
| F | 0.0102 | 68.7585 | 2 | .00 |

^{*}NS indicates not statistically significant.

ticularly in the context of the inappropriateness of identifying the "accident prone" individual in workplace injuries. 14

 χ^2 Analysis.—The following data in Table 1 can be used to illustrate the use of the χ^2 test for statistical analysis in this study: the observed number of initial bites and days of enrollment for infant males (eight bites; 1406 days of enrollment) and females (seven bites; 698 enrollment days), with a total for both sexes of 15 initial bites and 2104 enrollment days. The null hypothesis that is being tested is that the distribution of these bites is expected to be equal for both sexes; however, the number of days at risk for an initial bite (ie, the number of enrollment days) has to be taken into account in estimating the expected number of initial bites. The overall rate of initial bites per child day (ie, not the rate per 100 child days of enrollment) for both sexes combined was 0.0071 (15 bites ÷ 2104 enrollment days = 0.0071). This overall rate was multiplied by the number of enrollment days for each sex to compute the expected number of initial bites for males (ie, 0.0071×1406 male infant enrollment days = 9.9826 expected bites) and females (ie, 0.0071×698 female enrollment days = 4.9558 expected bites). The null hypothesis of no difference between sexes was thus tested with the standard χ^2 formula (with Yates' correction when df = 1), using the observed number of initial bites (eight and seven for males and females, respectively) and the expected number of initial bites (9.9826 and 4.9558, for males and females, respectively). The resulting χ^2 value (using Yates' correction for continuity) of 0.7014 is not statistically significant at the .05 level.

The values used to compute the expected number of bites within each of the groups studied (eg, the value of 0.0071 used to estimate the expected number of bites for males and females within the infant group), the χ^2 value, eg, 0.7014 in this example, the degrees of freedom, eg, df=1 in this example, and whether or not the results were statistically significant, are summarized for all of the χ^2 tests computed in this study in Table 2. This use of the χ^2 test for testing statistical significance in the numerator of a rate in which the denominator (eg, number of child days of enrollment) must be taken

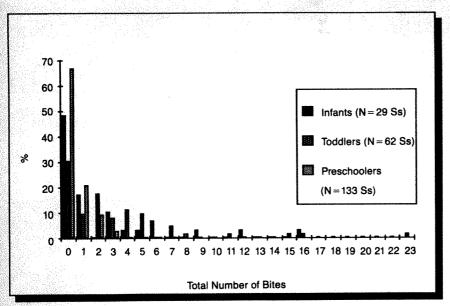


Fig 2.—Distribution of total bites by percent of children within each age group. Ss indicates subjects.

into account is a variation of a method used in survival analysis with exponential models. 15,16

RESULTS

Of the 224 children enrolled one or more days in the day-care center dur ing the 12 months of this study, 104 (46%) received one or more human bites, with a total of 347 bites reported for the year. As shown in Fig 2, the frequency of biting events within each age group varied from zero to 16 in the infant group, from zero to 23 in the toddler group, and from zero to seven in the preschool group.

Rates of Human Bites

Initial and total bites were statistically compared by age group for males and females separately and by gender within each age group. As shown in Table 1, the 104 initial bites in the day-care center during the study year were distributed as follows: 15 to infants, 43 to toddlers, and 46 to preschoolers. On average, there was slightly less than one initial bite per 100 days of enrollment for all subjects (based on 16219 enrollment days). (As shown in Table 1, this overall initial bite rate per 100 days of enrollment was 0.6412.)

There were no sex differences in the number of initial bites. Within the infant and toddler age groups, the females tended to have a slightly higher rate of initial bites than did males and within the preschool group, males had a slightly higher rate than females. As shown in Table 2, however, males and females did not differ statistically in the number of initial bites within the infant group $(\chi^2 = 0.7014,$ df=1), the toddler group ($\chi^2=0.7874$, df=1), or the preschool group ($\chi^2=$ 0.8522, df = 1).

The reader should note that the bite rates presented in Tables 1 and 2 represent the number of bites per 100 enrollment days, eg, an initial bite rate of 1.0029 for female infants. In other words, one bite per 100 days of enrollment for a female infant. However, the bite rates used to calculate the expected number of bites needed in the χ^2 test of significance are based on the rate per child day of enrollment, eg, 0.010029 for female infants. The initial bite rates per child day of enrollment also can be used to estimate the average number of days to the initial or first-time bite injury for a child within an age group. For example, if a toddler is enrolled full time in the day-care center, ie, 256 enrollment days, then the first biting injury could be expected to happen within 73 enrollment days (ie. $1.00 \div 0.0137$) on average, or more precisely, within 60 days if the toddler is a female $(1.00 \div 0.0231)$ and within 83 days if a male (1.00 ± 0.0367) .

The data in Table 1 show that toddler females had the highest rate of initial bite injuries per 100 enrollment days (1.6551) and the preschool females had the lowest (0.3299). If these rates had been constant for all bites throughout the year, then we could expect to see an average of approximately three bites per year (0.0120×256 enrollment days) for toddler males and four bites per year (0.0166×256) for toddler females; however, the initial rates were not representative of all biting incidents, as shown in the data on total bite rates in Table 3. When considered together, the data in Tables 1 and 3 show that, on average, female toddlers tended to be bitten initially within fewer number of days of enrollment, although toddler males tended to have the highest rate of total bites over a 12-month period.

There was a total of 347 bites in this day-care center during the study year, with 72, 195, and 80 total bites to infants, toddlers, and preschoolers, respectively. The number of total bites, days of enrollment, and the resulting rates per 100 child days of enrollment are given in Table 3, and the results of the χ^2 tests are summarized in Table 2. With a total of 23 771 days of enrollment throughout the study year, the total bite rate for all subjects in the day-care center was 0.014598 per child day of enrollment or, alternatively, approximately 1.5 total bites over 100 enrollment days. Another way of thinking about these results can be illustrated in the following example: if all 224 of these children in this day-care center had attended every day that the center was open (256 days) throughout the year, then based on the total bite rate per child day of enrollment (0.014598), we would expect to have seen a total of 837 bites by the end of the year (ie, $224 \times 256 \times 0.014598 =$ 837.1077). The fact that only 347 total bites were reported is due to the varying number of days in which children were enrolled at this center.

Were there differences due to the gender or the age group of the child based on the total bite rates? As shown in the lower half of Table 3, differences in total number of bites between males and females did not reach statistical significance in the infant ($\chi^2 = 1.6012$,

| | 2 1, 22 21 11 | Infant | | | Toddler | | | reschoole | r | Total | | | |
|------------------------------------|---------------|--------|--------|--------|---------|--------|--------|-----------|--------|--------|--------|--------|--|
| | М | F | Total | M | F | Total | M | F | Total | M | F | Total | |
| No. of children enrolled | 20 | 9 | 29 | 35 | 27 | 62 | 70 | 63 | 133 | 125 | 99 | 224 | |
| No. of total bites | 52 | 20 | 72 | 138 | 57 | 195 | 50 | 30 | 80 | 240 | 107 | 347 | |
| No. of child days enrollment | 2114 | 1169 | 3283 | 3762 | 2468 | 6230 | 7372 | 6886 | 14 258 | 13 248 | 10 523 | 23 771 | |
| Total bite rate per 100 child days | 2.4598 | 1.7109 | 2.1931 | 3.6683 | 2.3096 | 3.1300 | 0.6782 | 0.4357 | 0.5611 | 1.8116 | 1.0168 | 1.4598 | |

df=1) or preschool ($\chi^2=3.3207$, df=1) groups; however, the difference between sexes was statistically significant within the toddler group ($\chi^2=8.3610$, df=1, P<.01). In all three age groups, the males tended to have more total bites than expected, based on enrollment days in the day-care center, and the females tended to have fewer total bites than expected.

The total bite rates per child day can be used to estimate the average number of bites a child could expect to receive if he or she was enrolled in this day-care center over a specific period of time. For example, a toddler male could expect to be bitten an average of nine times if he were enrolled in this age group full-time in the center (0.0367×256 enrollment days), compared with a toddler female who could expect approximately six bites per year (0.0231×256), on average.

Was there a monthly variation of human bites in day-care centers? The total number of biting events for all children in the day-care center ranged from zero in February to 73 in August. Taking into account the number of child days of enrollment during each of the months, the rates varied from 0.000 in February to a high of 0.0335 per child day in September (compared with a rate per child day of 0.0317 for August). Thus, although there were actually more human bites reported in August, the rate was higher in September, as shown in Fig 3, especially among the toddler males. Differences among the three age groups by month were statistically significant (P < .001)based on a 3×12 χ^2 analysis $(\chi^2 = 281.18, df = 22)$. (In this analysis.) the expected values were computed on the basis of observed total rate per child day within each age group, ie, 0.0219, 0.0313, and 0.0056 for infants,

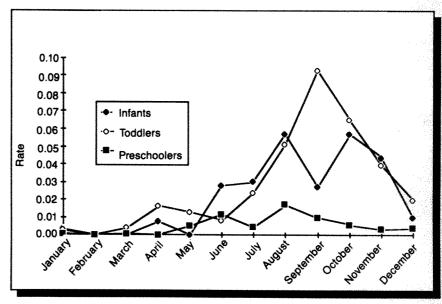


Fig 3.—Total bite rates per child day by month of injury and age group.

toddlers, and preschoolers, respectively.) The total bite rates per child day of enrollment for each age group are shown in Fig 3.

In other χ^2 analyses (not shown) of seasonal variations in initial bite rates per child day by sex, there was a statistically significant difference at the .001 level within each age group. Peak months for first-time bites were October for toddler males, August for toddler females, and July for infant males and females. Preschoolers tended to peak in June (females) and August (males). These data on initial bite rates, together with the data on total bite rates, suggest that the timing of staff in-service training about the prevention and treatment of human bites should be scheduled in May at this day-care center in anticipation of the upward trend in both kinds of bite rates over the ensuing five months.

Differences Between Children Who Were and Were Not Bitten

Did the children who were bitten tend to have any characteristics that distinguished them from those who were not bitten? Such information might be useful in identifying potential bite victims in a day-care center in the future and thereby preventing such incidents. Information on four variables was available in this study that permitted us to examine that question: age, sex, when the child enrolled in the center, and number of days enrolled during the study year. As shown in Table 4, those bitten did not differ from those not bitten in age (within age groups) within the infant or toddler groups; however, within the preschool group, the bite victims tended to be younger by almost 12 months, a difference that was statistically significant at the .0001 level

| Table 4.—M | oan Ago (in Days |) at End of Study Yea | ir |
|---------------------------|------------------|-----------------------|-------------|
| | Infant | Toddler | Preschooler |
| Bitten | 506 | 853 | 1329 |
| Not bitten | 516 | 871 | 1683 |
| Student's t test analysis | 0.1323 | 0.3704 | 4.8970 |
| ρ* | NS | NS | .0001 |

^{*}NS indicates not statistically significant

| Tall | olo 5Maan A | lumber of Engella | nent Days in Day-can | Center* |
|------------|-------------|-------------------|----------------------|----------------------------|
| | Infant | Toddler | Preschooler | All Age Groups Combined |
| Bitten | 179 | 125 | 128 | 134 |
| Not bitten | 44 | 50 | 98 | 84 |

Two-way analysis of variance: Age group: F = 2.79, df = 2/218, P = .064. Bitten/not: F = 33.85, df = 1/218, P<.001.

Interaction: F = 7.26, df = 2/218, P < .001.

| Table 6.— | Part of Body Bitten (B | ased on Percent of Total | al Bitos)* |
|-----------------|------------------------|--------------------------|------------|
| | infant | Toddler | Preschoole |
| Head | 4 | 11 | 5 |
| Upper extremity | 71 | 66 | 46 |
| Trunk | 0 | 11 | 15 |
| Lower extremity | 6 | 4 | 4 |
| Multiple parts | 0 | 2 | 0 |
| Unknown | 19 | 6 | 30 |
| Total, % | 100 | 100 | 100 |
| No. of bites | 72 | 195 | 80 |

 $^{^{*}\}chi^{2} = 40.55$, df = 10, P < .0001.

based on a Student's t test within each age group.

Males were no more likely to be bitten than females based on x2 analysis within each of the age groups. This finding is contrary to previous reports from physicians in which males were treated more often than females for human bites.

The admission policy of the day-care center permitted a child to enroll at any time if room was available in the appropriate age group. Differences in month of enrollment might suggest that a newcomer to a particular daycare setting might be more vulnerable to a human bite than a previously enrolled child; however, it was not possible to fully examine this possibility because the majority of subjects were already enrolled in the day-care center when the study year began. On the other hand, the total number of days of enrollment within an age group was

clearly associated with whether or not a child was bitten. As shown in Table 5, there was a statistically significant difference (P < .001) based on a two-way analysis of variance between all subjects in the center who were (N = 104)and were not bitten (N = 120). Those who were bitten had a higher number of mean days of enrollment (mean, 134 days of enrollment in the center) compared with those not bitten (mean, 84 days of enrollment). Although this variable did not differ statistically by age group, differences between those bitten and not bitten in terms of total number of months of enrollment tended to differ for the three age groups. For the infant group, this difference in length of enrollment at the center was approximately 41/2 months between bitten (N = 15) and not bitten (N = 14), followed by the toddler group with a difference of 21/2 months between bitten (N=43) and not bitten

(N=19), then by the preschool group that had a difference of approximately one month (bitten, N = 46; not bitten, N = 87). These differences within age groups could explain the statistically significant interaction effect (P < .001), as shown in Table 5.

Circumstances Surrounding the Biting Events

Information in the injury log that provided some clues about the circumstances surrounding the biting incidents based on total number of bites (N=347) included the activity of the subject when bitten, the child's geographic location when bitten, the body part bitten, and the treatment provided by staff. Thus, the focus of the analysis in this section was only on the children (N = 104) who were actually bitten.

The child's activity when he or she was bitten was recorded as "dispute with another child" in 94% or more of all bites; however, this prebite activity was inevitably identified after the biting event; thus, a recording bias is probably present. There were no statistically significant differences across age groups based on a χ^2 analysis. None of the bites in this study were self-inflicted nor were there any bites to a child by an adult.

When bitten, the majority of infants (99%) and toddlers (93%) were inside the day-care center; however, only 72% of the total biting incidents to preschoolers occurred inside the center. The other 28% of the preschooler bites occurred at a site away from the center, such as on a field trip or on a bus. This information could be useful to staff in alerting them to the increased risk of preschool bites while either in transit or on a group visit away from the day-care center. The difference across age groups was statistically significant at the .0001 level ($\chi^2 = 417.45$, df = 18).

The part of the body most often bitten was the upper extremities in infants (71%), toddlers (66%), and preschoolers (46%). As shown in Table 6. this distribution of total bites by body part was statistically significant $(\chi^2 = 40.55, df = 10, P < .0001)$ across age groups, with a large proportion of bites to preschoolers being recorded as "part of body bitten: unknown."

Once the staff were aware of a bite, the treatment consisted of the application of only ice or a cold pack for 47% of the infants and the majority of the toddlers (83%) and preschoolers (89%). Although information in the injury log did not indicate whether or not the skin was broken, most pediatrics textbooks¹ state that human bites should be cleansed.

The severity of the bite was also not described in the injury log; however, none of the children who received bites was taken to an emergency room or a physician as a result of the biting incident, as recorded in the injury log. As an additional piece of anecdotal information, the day-care staff did not ask the public health nurse who was the day-care consultant to the center on a monthly basis to examine any child because of a human bite nor did staff raise the possibility of infection due to human bites during the study year. The injury log did not include information about whether or not the parent was informed about the bite.

COMMENT

The results of this study have shown that almost half of all children in this day-care center received one or more human bites from another child while enrolled in the center over a one-year period and that toddlers received more human bites than did infants, and infants more than preschoolers. Although female toddlers tended to be bitten initially in a shorter period, on average, toddler males had the higher mean number of bites, based on total bite rates. None of the demographic characteristics available in the study, other than number of days of enrollment (and therefore number of days at risk), distinguished between those who were or were not bitten. The circumstances surrounding the biting incidents were sketchy in the injury log; however, there is the suggestion that the bites were not perceived as serious by the staff since none of the bite victims was taken to a hospital emergency room or a physician, nor (unfortunately) were the majority of bites to toddlers or preschoolers cleansed.

A major piece of information that was not recorded in the injury log was

the identification of the biter. Although this was not a study of the behavior of biters, the identity of the biter might be useful in preventing such injuries in the future, although other studies exist in the literature that examine the nature of the biting child.2 We suspect that there are at least six major areas of scientific study that could be developed in studying bites in day-care centers: the psychosocial behavior of biters themselves. the epidemiology of biters (including their rates of biting based on their number of days of exposure for carrying out such behavior), the psychosocial behavior of those bitten, interactions between biters and their victims, the emotional milieu of day-care centers that permit or prohibit biting, and the epidemiology of bites "received." This study has focused on the last issue, at one day-care center for one study year.

The major contribution of this study is the calculation of bite rates for children in day-care settings, data that, to our knowledge, have not been presented in the literature in the past. Given the considerable variation in number of days of enrollment as shown in this study, the use of number of children as the denominator in calculating such a rate seriously misrepresents the average number of bites per child. For example, if the rate among toddler males was the number of bites (138) divided by the number of children (35), then the average was 3.94 bites per year; however, by taking into account the number of enrollment days of all toddler males and the sex-specific age group-specific rate per child day (eg, 0.0367 for toddler males), the average number of bites per male toddler ranges from 9.39 for a full-time enrollee (256 enrollment days) to less than one bite (0.7340) for the male toddler enrolled full time for one month (20 enrollment days). Thus, in answer to a parent's query about the average number of bites his or her child could expect to receive, the health professional would have to ask how many days the child attends (or will be expected to attend) the center during a one-year period and then multiply that number by the sex-specific and age group-specific rate per child day.

The weaknesses of this study include the fact that this was a convenience sample of one day-care center (albeit all children enrolled in the daycare center were included in the study) and the generalizability of these results is therefore in question. As an initial study of epidemiologic rates, however, the role of studies using an N of 1 should not be underestimated in the continuous assessment of behavioral phenomena, as suggested by Kazdin and Tuma¹⁷ in their methodologic monograph on single-case research designs. Another weakness of this study is the problem of analyzing data that were accumulated for administrative purposes. Were the records accurate; did staff identify all biting incidents; were the events surrounding the injury accurately and consistently reported? These problems also exist in the research literature on workplace injuries, and clearly, carefully designed prospective research studies are needed. The assumption was made in this study that a human bite is sufficiently traumatic that such an event is usually made known immediately by the victim; therefore, the rates reported in this study are probably a good estimate of the events at this day-care center for this study year. The extent to which these rates apply to other centers has yet to be determined.

Human bites represent a potentially serious health hazard, and the issues raised in this study carry several policy implications. Should a parent be notified routinely by the day-care staff that his or her child has been bitten and the type of treatment that staff administered? Should there be a policy that all day-care staff are required to cleanse all human bites that occur in a day-care center whether the skin appears to be broken or not? Are the rates reported in this study at an "acceptable" level; acceptable to whomthe parent, the day-care provider, the health professional, or the child himself or herself? Can a day-care center expect to eradicate all biting incidents. or, if not, what is an acceptable level from a public health standpoint? Since there was no indication in this study that any of the biting incidents were regarded by day-care staff (who were not health professionals) as medically

serious enough to warrant a trip to a health facility for treatment, is it likely that human bites do not represent a potentially serious public health problem in day-care centers or, alternatively, has the problem had such little scientific investigation that the prevalence and seriousness of this kind of injury are unknown?

The transmission of infections via human bites represents another area of concern. The lack of epidemiologic data about human bites in day-care centers makes it difficult to estimate the actual risk that growing numbers of children face in the transmission of infections such as hepatitis B or, more remotely, the human immunodeficiency virus (HIV). There has been a report of transmission of hepatitis B due to human bites in an institutional setting.6 To our knowledge, a documented case of transmission of the HIV through a human bite has not been reported in the scientific literature: however, the legal and ethical issues raised in recent years due to concern about acquired immunodeficiency syndrome have implications for the collection and reporting of information about human bites in day-care centers. We want to reemphasize the fact that the severity of the bites reported in the injury log at this day-care center was not described; therefore, information about whether or not the skin was broken in these biting injuries was not available. This omission raises a question, however, concerning the type of information that needs to be recorded about a bite. Should day-care workers systematically re-

cord whether the skin is broken in a biting injury? Furthermore, should day-care centers be required to record the name of the biter, as well as the name of the victim, in all biting incidents? If so, what are the legal and ethical implications for the center, the parent of the biter, and the victim if a biter is later identified as a carrier of an infection such as HIV? How long should records of bites in day-care centers be maintained, if at all? Given increasing numbers of children enrolled in day-care centers, what is the role of the health professional in advising parents about the potential of human bites and their seriousness. and what is the role of the day-care center in notifying parents of prospective enrollees about the rate of bites or the expected number of bites a child is likely to receive at a particular center? These are only a few of the issues that have been raised by this study. Without additional research from the field regarding rates of human bites in daycare centers, the information needed to make informed decisions about these and other policy matters will not be available.

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Eugene Johnson and Chap Le gave statistical assistance.

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Quotables:

Writing: There's nothing to writing. All you do is sit down at a typewriter and open a vein.

RED SMITH

Management of Illness and Temporary Disability in Children Enrolled in Day-care Centers

The Health House Experience

Albert Chang, MD, MPH; Ana Zeledon-Friendly, MPH; Arlene Britt, RN, BSPNP; Bill Ewing, MA

 Alternative care arrangements are often necessary when children enrolled in day-care centers experience lilness or temporary disability. To meet this need, a new facility named Health House was established by the Child Development Program of the Pomona (Calif) Unified School District. This report describes the organization, operation, and costs of the program, and reviews the management of 179 episodes of illness or temporary disability in 99 children served by the program during the 1983-1984 school year. The medical conditions of patients cared for were comparable with those seen in physicians' offices as reported in a national survey. The daily cost of care per child for the sponsoring agency was \$38. The service enabled an average daily salary saving of \$39.80 for the working parent. Health House may serve as a model for the management of iliness or temporary disability in children enrolled in day-care centers.

(AJDC 1988;142:651-655)

The occurrence of illness or temporary disability (eg, recuperating from injury or surgery) in children enrolled in day-care centers (DCCs) often presents a significant management problem to both the parent and the day care provider. This is due to existing regulations in many states that require exclusion of ill children from the center. In addition, when children are ill or temporarily disabled, limitations in staff and facilities

may also preclude care in the regular center. At times, it may not be possible for the working parent to take time off to care for his or her child during an illness or disability episode. Parents, therefore, frequently face the stressful decision of either taking time off from work, with possible loss of salary or loss of job, or finding someone else to care for their children.

To deal with this problem, the following alternative care arrangements have been proposed: (1) care in the child's own home by a trained worker²; (2) care in a family day-care home³; (3) care in the child's own center with special provisions for care of ill children⁴; (4) care in a health facility designed for care of ill children (sometimes called the infirmary model)⁵; and (5) care in a separate DCC that only serves children with illness or temporary disability.

As an example of this last arrangement, a facility named Health House was established in December 1980 by the Pomona (Calif) Unified School District (PUSD). This facility is administered by the Child Development Program of the PUSD and funded by the California State Department of Education, and it serves children enrolled in the seven district-operated DCCs (enrollment range, 15 to 52 children; mean enrollment, 32 children). Health House provides care for children with illness or temporary disability who cannot be cared for at home by a parent and is open weekdays throughout the year.

This report will (1) describe the organization and services provided by Health House; (2) review the management of illness episodes encountered

during a nine-month period, ie, the school year from September 1983 to June 1984; and (3) calculate the program costs to the Child Development Program and the salary savings to the families served. We would like to share this information with other child health professionals considering developing a similar service.

PATIENTS AND METHODS Administration and Children Served

The PUSD serves a multiethnic population with an average daily enrollment of 22 600 students in the programs ranging from DCCs to high schools. Under the Child Development Program, child care is provided for children aged 6 weeks to 13 years in a variety of settings: Head Start classes, state preschool classes, an infant center serving adolescent mothers, and DCCs. At the inception of the Health House program, an administrative decision was made to serve only the children enrolled in the DCCs (and a few selected school-age children), since their families were judged to be in most need of the service. Table 1 shows the demographic and socioeconomic profile of the children enrolled (during midyear, March 1984) in the DCCs.

Health House occupies a large room adjacent to one of the DCCs and has been set up to physically resemble the other centers. It has a capacity for 12 children a day, and it is staffed by a head teacher and two parttime teacher aides. The staff supervises indoor activities, administers medications and/or special diets, and shares observations and information with parents about their child's condition. One of us (A.B.), the district's pediatric nurse practitioner (PNP), was assigned to the Child Development Program and works in Health House for two hours daily to screen the children and monitor their illness. The PNP is also available for telephone consultation during the rest of the school day. A pedia-

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trician in the community serves as a consultant to the district's health program. Because of the demand for the service provided, Health House is open from 6:30 AM to 5 PM.

When Health House was established, the administration was extremely cautious and established a very conservative policy for admission to the new program. Thus, children with suspected contagious illness are excluded from Health House as a precaution to prevent the spread of disease. These include children who show signs such as fever (oral temperature ≥37.8°C), diarrhea (defined as a watery stool), vomiting, or an undiagnosed rash. Nonetheless, children with conditions such as upper and lower respiratory tract infections, ear infections, and sore throats may be admitted to Health House when they are no longer considered contagious (following medical evaluation and treatment for 24 hours). Other children admitted to Health House include children with chronic conditions who experience an exacerbation (eg, asthma), children with injuries that require close observation and attention (eg, lacerations or serious contusions), and children recuperating from surgery. The PNP determines admissibility by examining the child or through a telephone consultation.

When a child becomes ill in the DCC, the PNP helps the head teacher complete an "Exclusion and/or Referral Form" (available from the authors on request) and sends the child home with written recommendations. Any child subsequently admitted to Health House who needs medication must have a section of this form signed and completed by a physician who provides information regarding the date of examination, diagnosis, special instructions, name of prescribed medicine, and dosage to be administered. There are some children, such as the asthmatic or allergic child, who have standing orders for medication valid for one calendar year. The PNP also has a special standing order for phenylpropanolamine hydrochloride-chlorpheniramine maleate syrup (Triaminic syrup). Every child who attends Health House has a medical file that includes a copy of the above-mentioned form, a release of liability form (signed by parent) for medication administration, and a medicine card used by the PNP to record the name of the medicine and dosage indicated by the physician. When a child comes to Health House his or her file is reviewed and updated with daily nurse's notes on the progress of the child's condition.

Study Sample

The study reviewed the Health House medical files of children served during the

Table 1.—Demographic and Socioeconomic Profile of Children Enrolled in Dey-care Centers (DCCs) and Children Served by Health House

| | % of | Children |
|------------------------|-----------------|-----------------------|
| , | DCCs* (n = 222) | Health House (n = 99) |
| Age, y | | |
| 2 | 12.6 | 10.1 |
| 3 | 46.4 | 42.4 |
| 4 | 31.5 | 26.3 |
| 5 | 9.5 | 21.9 |
| Sex | W. Santa | |
| F | 51.0 | 49.5 |
| М | 49.0 | 50.5 |
| Ethnicity | 46.8 | 41.4 |
| Black | | 36.4 |
| Hispanic | 32.0 | |
| White | 18.5 | 14.1 |
| Asian | 1.8 | 4.0 |
| Other | 0.9 | 3.0 |
| Family composition | | |
| Single mother | 75.6 | 64.6 |
| Both parents | 19.0 | 28.3 |
| Single father | 1.4 | 2.0 |
| Other | 4.0 | 5.5 |
| Monthly family incomet | | 70.8 |
| <\$1009 | 72.1 | |
| \$1009-\$1434 | 18.9 | 19.2 |
| >\$1434 | 9.0 | 10.1 |

^{*}Profile of children enrolled in DCCs in March 1984.

†Income eligibility levels used by school district for free (<\$1009) or subsidized (\$1009-\$1434) school lunch.

nine-month period from September 1983 to June 1984. Information was obtained regarding all illness episodes in these children. Two children whose files were incomplete as well as 15 school-age children were excluded from the study analysis. The latter group was excluded because they were not receiving day care on a full-time basis. The information analyzed for each illness episode included age, sex, ethnic group, family composition, symptoms and signs of illness, diagnoses (if available), management of the illness episode, duration of each illness episode, and duration of management at Health House. The classification of symptoms and diagnoses was based on a classification used for the past eight years by the PUSD Health Services Program (The Child Health and Disability Prevention Program, California's version of the Early, Periodic, Screening, Diagnosis and Treatment Program), which provides periodic health assessment from birth to age 21 years.

RESULTS Children in Study Sample

A total of 99 medical files of children who had experienced illness or temporary disability during the study period were abstracted. Table 1 shows the socioeconomic and demographic profile of the children who used Health House at least once. When compared with the total DCC enrollment, there were more 5-year-old children and children from two-parent families who used Health House, but other profile factors were similar.

The 99 children who were cared for at Health House experienced a total of 179 illness or disability episodes, an average of 1.8 episodes per child, with a range of one episode and a maximum of 11 illness episodes. Boys had 52.5% of the episodes and girls had 47.5%. The mean age of the children who experienced episodes was 3.7 years (SD, 1.033 years). The breakdown of ethnicity and parent composition per episode were similar to the study group (Table 1), with a high percentage of blacks and Hispanics (70.0%) and single mothers (60.0%). The PNP was responsible for most of the referrals to Health House; she referred the children in 122 (68.2%) of the episodes.

For the remainder, parents referred the children in 48 (26.8%) of the episodes and the DCC staff in nine (5.0%) of the episodes. The duration of an illness episode was defined as the chronologic number of days from admission to Health House until the last day in Health House. The average duration of an illness episode (excluding injury and recuperation episodes) was 9.5 days (range, one to 37 days). The average duration of an injury or recuperation episode was 18.4 days (range, five to 65 days). The average number of episodes per month was 17.9 (range, two to 30). More than the average number of episodes occurred during the colder months: October (20 episodes), January (19 episodes), February (28 episodes), March (23 episodes), April (18 episodes), and May (19 episodes).

Conditions Managed at Health House

Of the total 179 episodes managed at Health House, 153 (85.5%) were illnesses, 21 were injury episodes, and the remaining five episodes included children recuperating from surgery or being observed for possible asthma attacks. Tables 2 and 3, respectively, show symptoms and signs recorded by the PNP and diagnostic impressions of physicians of all illness and injury or recuperation episodes managed at Health House.

Management of Episodes at Health House

Of the total 179 patients who experienced episodes, 151 (84.4%) were given medication, 15 (8.4%) were placed on restricted activity, seven (3.9%) were placed on a special diet, and six (3.3%) received another type of management. Medical files showed that 147 (97.3%) of the 151 patients who experienced episodes were given medication, and written instructions from a physician were included. These medications included systemic antibiotics (81 episodes), a decongestant (35 episodes), medicine for asthma (17 episodes), eye/ear drops (11 episodes), and topical antibiotics (two episodes).

In 168 episodes (93.9%), the children were referred to a health practitioner. Of these, 160 (95.2%) carried out the

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| Symptom or Sign | No. (%) of Patients |
|--------------------------|------------------------|
| Cough with stuffy nose | 54 (25.9) |
| Earache | 36 (17.3) |
| Symptoms of injury | 21 (10.1) |
| Gasping for breath | |
| or wheezing | 19 (9.1) |
| Difficult or heavy | |
| breathing | 14 (6.7) |
| Sore throat | 14 (6.7) |
| Inflamed skin | 12 (5.8) |
| Inflamed eye | 12 (5.8) |
| Swollen tonsils | 8 (3.8) |
| Runny nose | 4 (1.9) |
| Painful urination | 3 (1.4) |
| Ear discomfort (chronic) | 2 (1.0) |
| Swollen mass in neck | 2 (1.0) |
| Other | 6 (2.9) |
| Not stated | 1 (0.5) |
| Total | 208 (100) |

*The total number of symptoms or signs is greater than 179 (total number of episodes) because some children showed more than one.

referral. The person who most frequently referred the child to an outside health resource was the PNP from Health House—she referred the children in 115 (64.2%) of the episodes.

Comparison of Health House Illness Episodes With National Ambulatory Medical Survey Data

To compare the characteristics of illness or disability episodes managed at Health House with episodes seen in practicing physicians' offices, the symptoms and diagnostic impressions of the episodes were compared with the findings of the 1980-1981 National Ambulatory Survey (NAMS).6 This comparison is shown in Table 4. The NAMS data shown are adjusted data excluding visits for "general medical examination" and "physical examination for school," since these were not reasons for admission to Health House. It should be noted that because of conditions excluded in Health House, the sign of "fever" (16.5% in the NAMS) and diagnoses such as "gastroenteritis" (1.8% in the NAMS) did not appear in the Health House statistics.

The statistics appear somewhat comparable, although cough (25.9% vs 12.4%), upper respiratory tract infection (24.5% vs 11.1%), and asthma (9.2% vs 2.8%) seem to be present more frequently in Health House than in the NAMS data.

Table 3.—Diagnoses of Children Cared for in Health House*

| | | | 100 |
|---------------------------|----|--------|-----|
| | | (%) of | |
| Diagnosis | Pa | tients | |
| Upper respiratory | | | |
| tract infection | 45 | (24.5) | |
| Otitis media | | (17.4) | |
| Asthma | 17 | (9.2) | |
| Lower respiratory | | ,, | |
| tract infection | 14 | (7.6) | |
| Streptococcal pharyngitis | | (7.1) | |
| Eye infection | | (6.5) | |
| Skin infection | | (6.0) | |
| Injury | | (4.9) | |
| Tonsillitis | | (3.8) | |
| Orthopedic problems | | (3.3) | |
| Eustachian tube | | · / | |
| dysfunction | 3 | (1.6) | - 7 |
| Other diagnoses | | (6.5) | |
| Not stated | | (1.6) | |
| Total | | (100) | |
| | | | |

*The total number of diagnoses is greater than 179 (total number of episodes) because some children had more than one.

Cost Analyses of Health House

Table 5 shows (1) cost of operation by service category ("instructional" includes the salaries of the Health House staff for the nine-month study period), (2) unit of service cost (cost of care per child per day), and (3) comparison of annual cost of Health House and annual salary savings to working parents. To show the economic benefits provided by Health House, the last item shows the costs (\$28424) incurred by the sponsoring agency for working parents with (\$38×748 days) and the potential salary savings (\$29 770) for parents made possible when their children were cared for in Health House (\$39.80) average daily wage of working parent × 748 days). The additional 371 unit costs (\$14098) were for services provided to children whose parents were in training programs and/or receiving AFDC (Aid to Families With Dependent Children).

COMMENT

This study describes the organization and experience of a separate DCC that provides care to children during periods of illness or temporary disability. It is one of several possible types of alternative care arrangements for children whose parents are unable to take time off from work or from other obligations.

The admission criteria in this cen-

Table 4.—Symptoms (or Signs) and Diagnoses Reported in Health House (1983-1984) and the National Ambulatory Medical Survey (NAMS) (1980-1981)*

| | % of Pat | ients |
|--------------------------------------|--------------|-------|
| | lealth House | NAMS* |
| Sympto | om or Sign | |
| Cough | 25.9 | 12.4 |
| Earache | 17.3 | 15.4 |
| Sore throat | 6.7 | 6.8 |
| Inflamed skin | 5.8 | 3.3 |
| Fever | NAT | 16.5 |
| | gnosis | |
| Upper respiratory tract infection | 24.5 | 11.1 |
| Otitis media | 17.4 | 21.6 |
| Asthma | 9.2 | 2.8 |
| Lower respiratory | * | |
| tract infection | 7.6 | 4.9 |
| Pharyngitis | 7.1 | 10.3 |
| Skin infections | 6.0 | 1.9 |
| Gastroenteritis | NA† | 1.8 |

*Adjusted data for children aged 2 to 5 years⁶ (see text for explanation).

†NA indicates not applicable (children with these conditions are excluded from Health House).

ter were, admittedly, very conservative: children who exhibited early signs of possible contagious disease (eg, fever, diarrhea, undiagnosed rash) were excluded. The conditions of the children admitted were rather more representative of minor illness or infection, eg, upper respiratory tract illness and ear infection. Children who had possible contagious diseases were admitted following medical evaluation and treatment for 24 hours, at which time they were not considered contagious. Clearly, this admission policy cannot be 100% effective in excluding a child with a possible contagious disease (eg, chickenpox or measles), but the experience described in this report did not show a failure of this screening procedure. The signs or symptoms and diagnoses of the conditions treated (Tables 2 and 3) were comparable with those conditions of young children seen in physicians' offices as reported in the 1980-1981 NAMS (Table 4). It should be noted, however, that the Health House data do show a higher percentage of children with cough, inflamed skin, upper respiratory tract infection, asthma, and skin infections.

| Tabi | ie 5.—Cost Analyses of Health H | louse | |
|-------------------------|---------------------------------|-------|----------|
| | | | Cost, \$ |
| Cost of operation by se | ervice category | | |
| Administration | - · · | - g/ | 5545 |
| Health services | | | 3498 |
| Instructional | | | 30 631 |
| Rent | | | 2854 |
| Total | | | 42 528 |
| Unit of service cost | | | |
| Total program cost | | | 42 528 |
| Units of service | | | 1119* |
| Unit of service cost | | 2.02 | 38† |
| | l cost of Health House and | | |
| annual salary saving | gs to working parents | | 1990 |
| Cost of Health Ho | | | 28 424‡ |
| Annual salary sav | | | 29 7706 |

*Number of days in which children were cared for for 6.5 hours or longer.

†This is a rounded figure

Calculated as \$38 × 748 days.

§Calculated as \$39.80 (average daily wage) × 748 days.

This variation may be due to the size of the Health House sample or to the admission patterns at Health House. For example, there may be a greater tendency to admit children with upper respiratory tract infections or with a known asthmatic condition without first requiring an evaluation by the child's physician if the child is known to have had these conditions previously.

Once a child was admitted to Health House, there was a high percentage of referrals for medical assessment (93.9%) and a high referral completion rate (95.2%). Review of the Health House and DCC health records demonstrated that every child showed progressive recovery except for one child with a known congenital heart condition who subsequently required hospitalization.

The cost analyses show that the cost of care in Health House for the sponsoring agency is higher (\$38 a day) than the current daily reimbursement the agency receives from the State Department of Education for children in its regular DCC (\$17.34 a day). The higher cost has been documented in other programs in which sick children are cared for. It should be noted that costs potentially could be higher since the rental cost of Health House (average, \$317 per month) was low compared with usual commercial rates. On the other hand, it should also be noted that the unit cost analysis (\$38 a day) was based on utilization rates that were less than full capacity during the year of the study. (Utilization rates have been progressively higher in subsequent years.) Potential units of service for an entire year were 2040 (170 days in academic year × 12 spaces). Thus, the 1165 units of service (1119 for DCC children plus 46 for schoolage children) provided in the study year represent only a 57.1% utilization rate. In theory, if every space had been used by a child with illness or temporary disability, the unit cost could have been decreased to \$20.84. The utilization variables (ie, the fluctuations of incidence of illness and temporary disability and family need for service) are, of course, beyond the control of the administrators of Health House. Furthermore, it is possible that a system of variable child spaces (eg, similar to hospital "swing beds") may reduce costs when the need for care of sick children is less due to seasonal variation, and personnel costs can be reduced. Another consideration for increasing utilization may be future changes of the admission guidelines that would allow additional children to be served, eg, children with mild or moderate fever.

Certain limitations of this study should be noted. Because it was a retrospective study, it is not possible to describe in detail the course of illness or disability in the children studied. In addition, it is not possible to compare the incidence of illness, management, outcome, and service costs of children cared for at Health House with children at other care

arrangements (eg, home with parents, relatives, or friends, family day-care home) since data for these variables were not collected. Thus, this report cannot serve as an evaluation of the program. A future study that can prospectively collect such information may determine the effectiveness and efficiency of the Health House model, compared with other models, in serving children with illness and temporary disability.

According to reports by K. B. Skold (Working Parents and the Problem of Sick Child Care: A report on the Issue for Local Grantmakers, unpublished data, July 1985) and Michaud (Children, Fall 1987, pp 67-69), there currently is great nationwide interest in providing services for day-care children when they are ill or temporarily disabled. There is an increasing number of programs being established. and several state licensing agencies are drafting regulations for the licensing of already-existing and future programs, according to the California Department of Social Services (Day Care Centers for Ill Children, unpublished data, 1986) and the Delaware Department of Social Services (DELACARE: Requirements for Sick Day Care in a Day Care Center, unpublished data, August 1986). We, in providing this report, do not wish to appear to give unqualified endorsement for the development of similar programs. We are aware of both medical and economic considerations for a cautious stance. Some have suggested that all children with illness or temporary disability (with the exception of highly contagious or life-threatening conditions) may be admitted to their regular DCC, provided proper staffing arrangements are made.4.7.8 But this policy is not generally considered acceptable at this time. Also, there is the potential that some programs may inappropriately serve certain children: some programs may care for children who are

really not ill at all or who may be too ill and require closer supervision than the center can provide. There is also genuine concern that some programs may arise mainly for economic considerations, eg, to use empty pediatric wards.9 Another concern is the potential psychological trauma experienced by children when temporarily placed in a new and different environment when they experience illness or disability. This has been a frequent concern we have heard, although there is no evidence documenting this as a serious problem for children and their families.

Clearly, another solution to this problem is the liberalization of parental leave during a child's illness or temporary disability. Legislation at both national and state levels has been introduced. Since this initiative will take time, the proposed alternative care arrangements may be considered by families with current needs.

As with other pediatric services, the best interests of the child and the family should be considered most important.9 There is no question that for many families, an acceptable alternative care arrangement (other than by the parent) is at times a necessity. Whether the establishment of services for ill or temporarily disabled children is safe, practical, and cost-effective will depend on the input of physicians, educators, and administrators; relative needs; and operating costs in each individual community and program. Consultation by physicians, especially pediatricians, will be essential in the planning of these services. 10

We would like to emphasize that the establishment of a care service such as Health House provides an additional benefit to families served by a DCC. Child care during an illness or temporary disability episode can be useful to parents who may have difficulty taking time off from work and other obligations. Another advantage

would be the reduction of conflict and guilt feelings in parents who know that their children are being well cared for. In addition, the potential for health education, health maintenance, and disease prevention activities is enhanced in a program that combines both preventive and treatment services, 11,12

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Quotables:

Writing: Writing is not a profession, but a vocation of unhappiness.

Georges Simenon

Failure of Hospitals to Promote the Use of Child Restraint Devices

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· Motor vehicle accidents are the leading cause of death in children. In 1977, Tennessee adopted the nation's first law requiring the use of child restraint devices (CRDs), but despite extensive promotional efforts, a majority of young children still travel unrestrained. We surveyed all acute-care hospitals in Tennessee to determine their policies regarding CRDs. Of 109 hospitals with obstetric services, 28 (26%) had a policy calling for discharged newborns to be transported in CRDs; only seven (5%) of 128 pediatric services had such a policy. It is time for hospitals and professional organizations to adopt policies to ensure that the parents of every child discharged from an obstetric or pediatric unit are educated concerning CRD use laws and are able to comply with them. Pediatricians should consider incorporating "discharge in child restraint device" into their routine discharge orders.

(AJDC 1988;142:656-658)

Injuries resulting from motor vehicle accidents are the leading cause of death in children of all ages beyond the perinatal period.1 In an effort to reduce motor vehicle injuries among children. Tennessee adopted the nation's first law requiring the use of child restraint devices (CRDs). Effective in January 1978, the law currently mandates the use of approved CRDs for all children younger than 4 years of age while being transported in a private vehicle. It has been shown that the use of CRDs provides a remarkable degree of protection from the risks of injury and death associated with motor vehicle accidents.24

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The proportion of children transported in CRDs in Tennessee rose from 8% in 19772 to 29% in 1980.5,6 Surveys indicate that statewide CRD use rates currently average 40% (unpublished data, Tennessee Department of Health and Environment, Nashville, April 1986). Thus, although the rate of CRD use continues to rise and is now five times greater than the baseline figure, a majority of children

still travel unprotected.

Inasmuch as the CRD law has been in effect for a decade and has been the subject of extensive publicity throughout that period, it appears that new intervention strategies are required to achieve universal use of CRDs. In this light, it is noteworthy that essentially all Tennessee children are born in a hospital (in 1985, 66257 [99.3%] of 66730 births; oral communication, Gail Casey, Tennessee Center for Health Statistics, June 1986). Thus, hospitals have the potential of providing a uniquely important opportunity for intervention to promote the use of CRDs for newborns and other children subject to the law. To determine the degree to which that potential was being realized, we surveyed all acutecare hospitals in Tennessee with pediatric or obstetric services to determine their policies and practices with respect to stimulating the use of CRDs for the newborns and young children discharged from their facilities.

METHODS

Records of the Tennessee Department of Health and Environment identified the 149 acute-care hospitals licensed in Tennessee as of Sept 1, 1985. A cover letter, questionnaire, copy of the Tennessee child restraint law, and return envelope were mailed to each hospital in January 1986. Telephone calls were placed to the administrative offices of those hospitals that had not responded by March 1986, and all outstanding questionnaires were completed at that

The 128 hospitals identifying themselves as providing obstetric or pediatric services were asked the following:

- 1. Does your facility require children under 4 years of age to leave the hospital in a federally approved child safety seat? If so, what action is taken when no CRD is available?
- 2. Does your facility provide an incentive program to encourage child safety seat use? If so, describe.

Licensing records were used to categorize each hospital as public, private nonprofit, or private profit-making (proprietary) and to determine the number of licensed beds. Each hospital was assigned a score reflecting relevant medical school affiliations, determined by tabulating the number of times each hospital was listed in the 1986-87 Directory of Residency Training Programs, as a principal participating institution for a medical school pediatric, obstetric, or family practice residency training program.

Univariate statistical testing was done by calculating χ^2 or Fisher's exact tests and odds ratios (ORs), the x2 test for trend, and 95% confidence intervals (CIs), as appropriate.8 Continuity corrections were used. Logistic regression was done using the LR module of the BMDP statistical package (BMDP Statistical Software, Los Angeles).

RESULTS **CRD Policy**

Of the 128 hospitals, 100 (78%) had no policy regarding the use of CRDs by discharged patients under age 4 years leaving by automobile (Table 1). Twenty-one hospitals (16%) had a policy calling for the use of CRDs for newborns but not other patients under age 4 years; an additional seven hospitals (5%) required that all patients under age 4 years, including newborns, be discharged in CRDs. A policy regarding CRD use for discharged patients existed for 28 (26%) of the 109 surveyed obstetric services, compared with only seven (5%) of the 128 surveyed pediatric services (OR = 6;

Table 1.—Presence of Childhood Restraint Device (CRD) Policies or Incentive/ Educational Programs at 128 Surveyed Hospitals

| | No | . (%) |
|--|-------|---------|
| Characteristic | of Ho | spitals |
| All hospitals (n = 128) | | |
| Policy regarding CRD use at discharge | 28 | (22) |
| Supplied CRD, if needed, to enforce policy | 10 | (8) |
| Offered incentive or educational program* | 38 | (30) |
| Obstetric services (n = 109) | | |
| Policy regarding CRD use at discharge | 28 | (26) |
| Supplied CRD, if needed, to enforce policy | 10 | (8) |
| Pediatric services (n = 128) | | |
| Policy regarding CRD use at discharge | 7 | (5) |
| Supplied CRD, if needed, to enforce policy | 4 | (3) |

^{*}The majority of these programs were targeted at parents of newborns.

95% CI = 2.7, 13.3).

Characteristics of the 128 hospitals are summarized in Table 2. There was an association between increasing hospital size and a policy regarding CRD use: 16% of small hospitals, 25% of medium-sized hospitals, and 37% of large hospitals had such a policy (x2 test for trend, P = .04). Although proprietary hospitals were somewhat less likely to require CRD use than public or nonprofit hospitals (18% vs 25% and 24%, respectively), the difference was not statistically significant. Hospitals with medical school-affiliated pediatric, obstetric, or family practice residency programs were three times more likely to require the use of CRDs than hospitals without such affiliations; 19% of hospitals with no such affiliations had a CRD requirement, compared with 25% of those with one such affiliation and 67% of those with two such affiliations (P = .01). When size, hospital type, and affiliations were tested against CRD requirement in a logistic regression model, the only variable to remain significantly associated was the number of medical school affiliations (P = .02).

Enforcement of Policy

Of the 28 hospitals with a CRD policy, ten stated that they would, if necessary, provide a CRD to ensure their policy was complied with; the remaining 18 waived their requirement if the parents were not prepared to comply. Affiliation with a medical school correlated with the willingness to provide CRDs in order not to waive a CRD requirement: 73% of hospitals with no affiliations waived their re-

quirements, compared with 50% of hospitals with one affiliation and 33% of hospitals with two affiliations (P=.06). Of the 21 hospitals whose CRD requirement was restricted to newborns, six (29%) were prepared to supply CRDs if necessary. In contrast, of the seven hospitals requiring CRD use by all discharged patients under age 4 years, four (57%) would supply the CRD if necessary (OR=3.3; 95% CI=0.6, 19.4).

Educational Programs

Of the 128 hospitals, 38 (30%) offered an incentive or educational program designed to encourage the use of CRDs (Table 1). Small hospitals were much less likely to offer such a program: 17% of hospitals with 100 or fewer beds offered such a program, compared with 43% of medium-sized and 47% of large hospitals (OR = 0.27; P = .002). Most programs were oriented toward educating patients on the obstetric, rather than pediatric, service, as is illustrated by the fact that the presence of such a program was much more likely in a hospital with an obstetric service. Of the 109 hospitals caring for newborns, 36 (33%) offered a program, compared with only two (11%) of the 19 hospitals not caring for newborns (OR = 4.2): 95% CI = 1.0, 17.4). Programs were more often found in hospitals with medical school affiliations: 50% of hospitals with one or more affiliations had a program, compared with 27% of those with no affiliations (OR = 2.7; 95% CI = 0.9, 8.0).

Interestingly, hospitals requiring CRD use appeared to be only some-

| | -Characteristics of 128 Acute-Care Hospitals | | |
|--|---|------------------|--|
| Characteristic | | . (%) spitals | |
| Clinical services Pediatric | 128 | (100) | |
| Obstetric | 109 | (85) | |
| No. of licensed bads 20-100 (small) | 69 | (54) | |
| 101-300 (medium) | 40 | (31) | |
| 301-2068 (large) | 19 | (15) | |
| Type of hospital Public | 44 | (34) | |
| Private, nonprofit | 33 | (26) | |
| Proprietary | 51 | (40) | |
| No. of medical school affiliations* | | | |
| 0 | 114 | (89) | |
| 1 | 8 | (6) (5) | |

*Number of times hospital was listed as a principal participating institution for a medical school residency program in obstetrics, pediatrics, or family practice.

what more likely to offer an educational or incentive program promoting CRD use: 11 (40%) of the 28 hospitals with a CRD policy offered a program, compared with 27 (27%) of the 100 hospitals with no policy (OR = 1.75; 95% CI = 0.7, 4.2). Indeed, logistic regression modeling indicated that of the variables studied, hospital size and presence of an obstetric service were the only independent predictors of the presence of an educational program.

COMMENT

Tennessee was the first state to mandate the use of CRDs. In the subsequent decade, the citizens of Tennessee have been exposed to extensive publicity concerning the CRD law, reports of its efficacy, 2,5,6 and news of the adoption of similar laws in each of the other 49 states, as well as to increasingly active enforcement of the CRD law by the Tennessee Highway Patrol² and to a continual series of public education programs sponsored by the Tennessee Department of Health and Environment and other groups. Despite all of this, observational surveys indicate that the majority of children under age 4 years still do not travel in a CRD. It is clear that efforts to promote CRD use have not been adequately effective.

An effective and efficient interven-

tion program should reach the entire target population, and only the target population; it should do so at an appropriate time with respect to the need being addressed, and it should do so under circumstances conducive to the desired intervention. By these criteria, it is hard to imagine a more ideal setting for a CRD intervention program than that available in hospitals with maternity services. A comprehensive hospital-based CRD intervention program would reach essentially every mother, and many fathers, at a time when they are already receiving-indeed, are eager for-guidance regarding the care of their newborn. The American Academy of Pediatrics (AAP) recognized the importance of such an approach with its "First Ride-Safe Ride" program, launched in 1980. Similar programs targeted at pediatric patients would serve to reinforce the prior education.

Unfortunately, our data indicate that few hospitals yet are taking appropriate action to promote the use of CRDs. Only one fourth of the surveyed hospitals offering obstetric services had a policy regarding CRD use by discharged newborns. The performance on the pediatric services was even more dismal: only 5% had a CRD policy. Furthermore, most hospitals with a CRD use policy would waive that "policy" if the parents did not provide their own CRD at the time of discharge. Only one third of the hospitals offered a program designed to promote the use of CRDs; these promotional programs most often were targeted at the parents of newborns and did not reach the parents of other pediatric patients.

It has been shown that hospitalbased CRD intervention programs are capable of producing dramatic increases in CRD use rates. 10-12 Although some studies have shown that CRD use among recipients of these intervention programs was no longer significantly greater than that among persons not receiving the intervention after a period of several weeks to months, 10-18 that change was often due more to increases in CRD use among the control group than to a decline among the intervention group. 10,13 Furthermore, many of the studies showing a drop-off in CRD use with time following intervention were performed before the establishment of a local CRD use law. In the current climate of universal CRD use laws and widespread publicity regarding the issue, it may be that hospital-based CRD intervention programs would lead to even larger and more durable increases in CRD use rates.

The potential of a statewide hospital-based CRD intervention program has been illustrated in Vermont, where a volunteer-staffed program of educational activities and CRD rentals was associated with an increase in the use of CRDs at hospital discharge from 16% to 71%, despite the absence of a CRD law.11 More recently, the Pennsylvania Chapter of the AAP has coordinated a CRD promotional program targeted at hospitals, which are required by Pennsylvania law to provide CRD information and CRD loaner program referrals to the parents of newborns. As a result, a number of Pennsylvania hospitals now offer free

or low-cost CRDs to the parents of newborns (oral communication, Suzanne Yunghans, BSW, Pennsylvania Chapter, AAP, June 1986). This is an encouraging development, and other states may wish to adopt similar requirements.

Although previous studies have indicated that intervention programs based in physicians' offices13-16 or public clinics17 can lead to increased CRD use, such an approach offers neither the timeliness nor the universality available with a hospital-based system and thus may be more suitable for reinforcement than initiation of CRD use. In addition, only a minority of physicians caring for young children have yet incorporated CRD promotional activities into their practices. 16,18 As a practical matter, it would be far simpler to establish a comprehensive intervention program through hospitals than through physicians' offices or clinics.

Laws concerning CRD use are now in place in every state. It is time for the appropriate hospital and professional organizations to adopt policies designed to ensure that the parents of every child discharged from an obstetric or pediatric unit are educated about, and are able to comply with, local regulations regarding the use of CRDs. The promotion of CRD use should be a clearly recognized element of the standard of pediatric and obstetric care. Pediatricians should support such programs through their hospital's medical staff and should consider incorporating "discharge in child restraint device" into their routine discharge orders.

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Labial Adhesions and Posterior Fourchette Injuries in Childhood Sexual Abuse

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 Six cases involving six sisters, all of whom were sexually molested, are presented to illustrate the association between lablal adhesions and posterior fourchette injuries in sexually abused children. Although labial adhesions are a relatively common lesion, they only recently have been associated with childhood sexual abuse. Lablal adhesions are ordinarily found in girls between 2 months and 7 years of age and are usually very superficial and disappear spontaneously by the time the child approaches puberty. We encountered six sisters, all of whom had been sexually abused, who had lablal adhesions. Four of the six had changes in the area of the posterior fourchette that were consistent with previous trauma. In addition, four of the girls' hymens had thickened, irregular edges or other changes that were considered abnormal. The father, the grandfather, and an uncle confessed to lewd and lascivious misconduct with the children. Although labial adhesions alone are not reason enough to make a report of sexual abuse, the physician is obligated to inquire as to the possible cause if the adhesions do not fit the usual pattern or If there are other suspicious findings.

(AJDC 1988;142:659-663)

The search for findings that may be considered conclusive physical evidence of sexual abuse in children suspected of having been molested is a difficult and oftentimes a perplexing task. Such an investigation is hampered by the fact that the actual cause of many of the minor differences noted in the genitalia of children is unknown. There is speculation that injuries to the perineum can be caused by such activities as horseback riding and gymnastics. Because well-designed,

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controlled studies that could document the changes in the anatomy of young girls brought about by these and other activities are unavailable, we are frequently left with individual case reports that then must be used to form the basis of medical opinion.

A relatively common finding that has been described in the medical literature1,2 for years is that of labial adhesions. Although this entity has been ascribed to "poor hygiene and hypoestrogenism,"1 this finding, with or without evidence of previous injury of the posterior fourchette, has only recently been described as possibly being caused by sexual abuse. We herein describe six sisters, who, following sexual molestation by their father, grandfather, and uncle, had labial adhesions and signs of trauma to the region of the posterior fourchette.

PATIENT REPORT

Six girls, ranging from 4 to 9 years of age, were removed from their parents' home by the Children's Protective Service, Fresno, Calif, following an investigation of possible abuse and neglect that had originated in another state. At the time, the caseworker and a law enforcement officer visited this family and found the girls with their mother, father, grandfather, and uncle, all living in a mobile home. The children, in addition to very poor hygiene, had a variety of untreated medical conditions.

Initially, three of the six sisters were described as being very withdrawn and fearful. Two of them had problems with enuresis and one with encopresis. As they became more familiar with their new surroundings, two of the girls began talking about how they had been sexually molested by their father, grandfather, and uncle. According to the children, this included fondling, oral copulation, and attempted intercourse. The 5-year-old described bleeding from her "wee wee" following one of these episodes.

The children were examined in the Childhood Sexual Abuse Clinic at Valley Medical Center, Fresno, Calif. The examination included a history, a complete physical examination, and a colposcopic examination, with magnified photographs of the external genitalia. Cultures of the pharynx, vagina, and rectum for the presence of gonorrhea were obtained, and a serologic rapid plasma reagin (RPR) card test for syphilis was performed. Normal saline wet mounts and potassium hydroxide preparations collected from the three older girls yielded normal results. All of the cultures for Neisseria gonorrhoeae proved to be negative, with no reaction on any of the RPR tests. Chlamydial cultures were not being done routinely at the time these children were examined.

The girls' genitalia revealed a variety of findings that were believed to be consistent with childhood sexual molestation. All of the girls were still in the Tanner stage I of secondary sexual development. The hymen of the oldest sister, who was 9 years 7 months of age, had a very irregular border and thickened, rolled edges (Fig 1). The vascular pattern was disrupted, and the hymenal orifice measured 10×6 mm in the vertical and horizontal planes in the kneechest position. The posterior hymenal rim was relatively narrow. A combination of an adhesion, with some scar formation and an abnormal vascular pattern, was present in the area of the posterior fourchette.

The 8-year-2-month-old sister had an extensive 10-mm-long, thickened, irregular adhesion of the posterior fourchette (Fig 2). Although the edges of her hymen were smooth and thin, she had a relatively thick midline hymenal septum that had not been disrupted. She did have a mild form of cerebral palsy that was believed to be secondary to a congenital herpes infection.

The 7-year-2-month-old sister's hymen was smooth-edged and symmetrical but was moderately thickened, with an increase in its vascularity. The transhymenal diameter in the knee-chest position was 6×6 mm in the vertical and horizontal planes, respectively. However, she did have a 6-mm healing lesion of the posterior

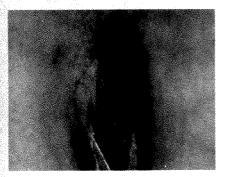


Fig 1.—Colposcopic photograph of 9-year-7-month-old sister in knee-chest position, with 6-mm labial adhesion and posterior fourchette scar. Hymen is irregular with hymenal orifice of 10 × 6 mm in vertical and horizontal planes (original magnification, × 5)

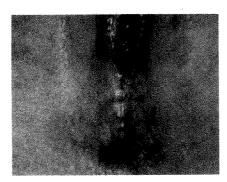


Fig 2.—Colposcopic photograph of 8-year-2-month-old sister in supine position, with 10-mm thickened and irregular labial adhesion and posterior fourchette scar (original magnification, \times 5).



Fig 3.—Colposcopic photograph of 7-year-2-month-old sister, with 6-mm posterior fourchette adhesion and scar deviated to left of midline. Hymenal edges are thickened and rolled, with abnormal vascular pattern (original magnification, \times 5).

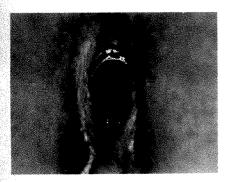


Fig 4.—Colposcopic photograph of 6-year-1-month-old sister in knee-chest position, with hymenal orifice 10×7 mm in vertical and horizontal planes. Narrow hymenal rim with thickened rolled edges (original magnification, $\times5$).

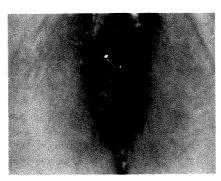


Fig 5.—Colposcopic photograph of 6-year-1-month-old sister in supine position, with 5-mm labial adhesion, with neovascularization over posterior fourchette (original magnification, ×5).

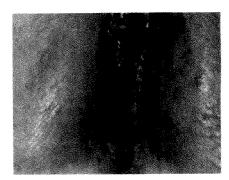


Fig 6.—Colposcopic photograph of 5-yearold sister in supine position, with 8-mm labial adhesion and neovascularization (original magnification, \times 5).

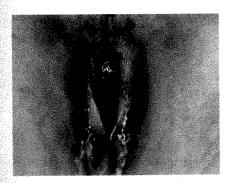


Fig 7.—Colposcopic photograph of 5-yearold sister in knee-chest position showing thickened, irregular hymen, with an adhesion/scar to left of midline in 12-o'clock position and history of vaginal bleeding (original magnification, ×5).

fourchette that deviated to the left of the midline and appeared to be a scar (Fig 3). A moderate amount of neovascularization surrounded the lesion.

The 6-year-1-month-old sister's hymen consisted of a relatively narrow rim of



Fig 8.—Colposcopic photograph of 4-year-old sister in knee-chest position, with normal hymen. Avascular midline lesion in posterior fourchette/navicular fossa appears in region of labial adhesion (original magnification, \times 5).

tissue with rolled edges. The vascular pattern appeared to have been disrupted. The hymenal orifice's vertical and horizontal diameters measured 10×7 mm, respectively, in the knee-chest position (Fig 4). In the supine position, there was an irreg-

ularity of the posterior fourchette with a concomitant adhesion that was 5 mm long. The neovascularization in this area did not cross the midline (Fig 5).

The most dramatic changes were seen in the 5-year-old sister. In addition to an 8-mm-long labial adhesion (Fig 6), there was a scar on the hymen in the 6-o'clock position that created an irregularity of its anterior edge. The hymenal edges were thickened and rolled, with an abnormal vascular pattern present throughout the surface of this membrane (Fig 7).

The findings in the 4-year-old sister were normal. Her hymen was smooth-edged and symmetrical. The vascular pattern was normal, and there was an ample rim of tissue at the posterior attachment (Fig 8). The hymenal span was 6×3 mm in the vertical and horizontal planes when measured in the knee-chest position. A relatively superficial labial adhesion (2 mm long) was discovered in the posterior four-chette, which in the knee-chest position took on the appearance of a midline avascular area.

| | Findings in Sister by Age, y (mo) | | | | no) | |
|---|-----------------------------------|---------------|----------|---------------|---------------|---------------|
| | 4 (0) | 5 (0) | 6 (1) | 7 (2) | 8 (2) | 9 (7) |
| Described molestation | No | Yes | Yes | Yes | No | Yes |
| Cries easily | No | Yes | No | Yes | Yes | Yes |
| Withdrawn | No | Yes | No | No | Yes | Yes |
| Fearful of men | No | No | Yes | Yes | No | Yes |
| Diurnal enuresis | Yes | No | Yes | No | No | No |
| Encopresis | No | Yes | No | No | No | No |
| History of vaginal bleeding | No | Yes | No | No | No | No |
| Hymenal orifice diameter, mm Supine vertical | 6 | 1* | 5 | 4 | , † | 7 |
| Supine horizontal | 4 | 1* | 3 | 3 | † | 5 |
| Knee-chest vertical | 6 | 7 | 10 | 6 | 8 | 10 |
| Knee-chest horizontal | 3 | 3 | 7 | 6 | 4 | 6 |
| Hymenal edge | Smooth | Irregular | Rolled | Rolled | Septum | Irregular |
| Hymenal membrane | Redundant | Thick/scar | Thin | Thick | Thin | Thin |
| Abnormal vascular pattern | No | Yes | Yes | Yes | No | Yes |
| Width of hymenal rim (6-o'clock position), mm | 3 | 3 | 1.5 | 3 | 3 | 1 |
| Length of labial adhesion/scar, mm | 2 | 8 | 5 | 6 | 10 | 6 |
| Posterior fourchette lesion | Adhesion | Adhesion/scar | Adhesion | Adhesion/scar | Adhesion/scar | Adhesion/scar |

*Not relaxed.

†We were unable to determine vaginal orifice diameters in the supine position in the 8-year-old sister.

After the disclosures by the children and the presentation of the physical findings, the mother began describing how the children had been molested by her husband, father-in-law, and brother-in-law. Subsequently, all three men confessed to California Penal Code Section 288, lewd and lascivious misconduct with the children.

The Table summarizes the behavioral changes and the physical findings in the six sisters.

COMMENT

Many authors have stated that in cases of childhood sexual molestation, the physical examination frequently yields normal results.3-5 As investigators have gained greater expertise and improved their techniques of examining preadolescent children, an increasing number of physical findings are being attributed to the act of sexual abuse. The addition of the colposcope has added yet another dimension to the investigation of these allegations. This instrument, with its multiple lenses that magnify a suspicious area, a green filter that assists in the examination of a vascular bed, and an attached camera to record the findings, has provided the practitioner with a powerful tool.6,7 The difficulty with many of the findings detected during these examinations is that

there are relatively few well-controlled studies to assist in the determination of whether a finding is normal or abnormal.

The common denominator of the labial adhesions found in the children in this report is not that unusual a finding by itself.8-15 Although labial adhesions have been described for years in the medical literature, they have only recently been associated with childhood sexual abuse.2 Since the first report in the American literature in 1936 by Nowlin and Adams,8 there have been numerous articles9-15 describing the incidence, physical findings, possible cause, and treatment. Labial adhesions have been called various names, including labial agglutination, vulvar fusion, vulvar synechiae, gynatresia, coalescence of the labia minora, and occlusion of the vaginal vestibule. The most commonly accepted explanation is that the lesions are caused by local inflammation, usually as a result of poor hygiene, a mild vulvitis, or mechanical irritation along with the state of hypoestrogenism. 1,9-11

Labial adhesions are usually seen in girls between 2 months and 7 years of age, with the majority of cases noted before the age of 2 years. 12 Although these are not uncommon lesions to the

practitioner, the incidence, as observed in Denmark in a study by Christensen and Oster, 10 was found to be only 1.4%. However, Emans et al16 reported an incidence of 21% in their study of nonabused white children. There is a general agreement that these adhesions usually are very superficial gossamerlike, semitransparent membranes that are easily disrupted by gentle lateral traction of the labia.8-11 According to Finlay11 and others, this procedure results in minimal discomfort to the child, with little if any bleeding from the surface of the separated labia. The recurrence rate appears to be significantly reduced by the application of a lubricant or an ointment containing estrogen. 10-15 Many authors believe that since these lesions are self-limiting and disappear as the girl approaches puberty, no treatment is required if the child is asymptomatic.

If a decision is made to treat the labial adhesion, the physician needs to be aware of the complications that may occur as a result of therapy. If repeated applications of estrogen cream are applied to the labia, the child may absorb enough of the steroid to develop premature thelarche, which may lead to concern about a more serious under-

lying disease process.² If lubricants or estrogen creams are not used and repeated mechanical separation of the adhesion is performed, a thick scar may form that involves the deeper layers of the epidermis. These scars then may not automatically lyse as the child enters puberty.

Injuries to the posterior fourchette can result from a variety of causes. It has been postulated that girls "doing the splits, riding horseback or participating in gymnastics may sustain an injury to the tissues of the posterior fourchette." The epithelial layer in this area does separate easily and may be disrupted during a medical examination if too much lateral traction is applied to the region. However, injuries to the posterior fourchette have also been reported to occur as a result of intracrural or intralabial intercourse."

In our experience, the changes seen in the posterior fourchette in children who have been sexually abused have varied from relatively minor increases in vascularity to deep lacerations extending to the anus. The most common form of injury that we have attributed to these acts are healed lesions that frequently deviate to one side or the other of the midline and involve the navicular fossa. The increase in vascularity seen with these lesions usually does not cross the midline.

The labial adhesions in these sisters ranged in size from the 2-mm-long adhesion in the 4-year-old sister (Fig 8), which only became evident during the colposcopic examination, to the 10mm-long lesion in the 8-year-old sister (Fig 2), which was easily detected during the macroscopic portion of the physical examination. In the three younger children, the adhesions appeared to be very superficial and somewhat transparent (Figs 5 through 8). This latter appearance is the type that is described in the literature, and we do not see an association with childhood sexual abuse.

However, the findings in the children described herein differ in several ways from the usual case of labial adhesions. The fact that all six of the girls had a variation of labial adhesions is remarkable by itself. Although labial adhesions are not uncommon le-

sions, there is only one article¹⁸ in the literature that describes labial agglutinations in sisters; in that case, only two girls were involved. Another unusual finding was the ages of the girls. Since labial adhesions are usually seen in girls between 2 months and 7 years of age, it is of interest that two of the six sisters were 8 and 9 years old, respectively (Figs 1 and 2).

The most significant difference was the type of adhesion seen in four of the girls. In the 8-year-old sister, the adhesion appeared to be thick and irregular in texture and was similar in appearance to the type of scar tissue seen in children who have had their adhesions forcefully disrupted on multiple occasions. The lesions of the posterior fourchette found in the 5-, 7-, and 9-year-old sisters not only appeared to involve the deeper tissue layers but also deviated to the left of the midline and were accompanied by relatively large blood vessels that did not cross the midline.

Distinguishing adhesions from scars may be difficult, particularly without a tissue biopsy. Since the usual labial adhesion consists of a superficial attachment of the two inner surfaces of the labia minora, it has the appearance of a thin, smooth membrane. Scars, on the other hand, involve the deeper layers of the tissues and appear thick and irregular. A combination of these findings was seen in four of the sisters whose labial adhesions also appeared to include a significant amount of scar tissue.

Scars in this region must be distinguished from the naturally occurring midline perinei raphe overlying the perineal body. A raphe, when present, frequently appears as a slightly elevated midline ridge of tissue that runs from the posterior fourchette to the anus and marks the union of these tissues that occurred during the embryonic phase of the child's development. Ordinarily, there is no increase in vascularity in the area.

The children in this report were examined in both the supine and knee-chest positions. Although the adhesions of their labia were best visualized in the supine position, the kneechest method proved to be of value in the examination of their vaginal canals

and hymens. In the knee-chest position, the relatively free-floating anterior wall of the prepubertal child's vagina falls forward, opening the introitus and the canal. With the use of a bright light and a magnifying lens. the entire canal, including the cervix. can usually be seen. In the child in whom child abuse is suspected, this position also offers an excellent view of the hymen due to the fact that the major portion of the hymen is attached to the posterior and lateral rims of the vaginal introitus. As the girl assumes a prone posture, this membrane falls forward, stretching out under its own weight. In this configuration, changes in the vascular bed or alterations of its contour become readily apparent.

In this case, the edges of the hymen of the 5- and 9-year-old sisters proved to be grossly irregular when they were placed in the knee-chest position (Figs 1 and 7). The distortion of the anterior edge and body of the hymen in the 5year-old sister appeared to have been caused by scar tissue that most likely resulted from a previous transsection of this membrane. The hymens of the 6- and 7-year-old sisters were found to consist of only narrow rims of tissue with rolled edges and distorted vascular patterns (Fig 4). These findings were considered to be consistent with the history of childhood sexual abuse.

The association between childhood sexual molestation and labial adhesions can only be surmised. In these children, the diagnosis of sexual abuse appeared certain even without the confessions by the male members of the family or the description of the acts by the mother. The fact that there were adhesions or scars of the posterior fourchette only added to the preponderence of evidence.

Labial adhesions alone should not warrant an automatic referral to a law enforcement agency or the Children's Protective Service; however, the physician has an obligation to inquire as to the cause, particularly if the adhesions do not fit the usual pattern or if there are other suspicious findings.

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in Other AMA Journals

ARCHIVES OF DERMATOLOGY

Pathogenesis, Clinical Features, and Management of the Nondermatological Complications of Epidermolysis Bullosa

John E. Craighead, MD (Arch Dermatol 1988;124:705)

Clinicopathologic Types of Epidermolysis Bullosa and Their Nondermatological Complications

Roger W. Pearson, MD (Arch Dermatol 1988;124:718-725)

Gastrointestinal Manifestations of Epidermolysis Bullosa in Children Joyce D. Gryboski, MD; Robert Touloukian, MD; Ruth A. Campanella, MD (Arch Dermatol 1988;124:760-761)

Acquired Progressive Lymphangioma as a Flat Erythematous Patch on the Abdominal Wall of a Child

Takayoshi Tadaki, MD; Setsuya Aiba, MD; Shinichi Masu, MD; Hachiro Tagami, MD (Arch Dermatol 1988;124:699-701)

An Atlas of Pediatric Dermatology by Meneghini and Bonifazi Reviewed by Karen McCoy, MD (Arch Dermatol 1988;124:787)

New Child Abuse Spectrum in an Era of **Increased Awareness**

William N. Marshall, Jr, MD; Terry Puls, MSW, ACSW; Carol Davidson

 Three hundred eighty-two children were evaluated for abuse or neglect during a 30-month period in a pediatric clinic in a county hospital. Fifty-one percent presented for sexual abuse, 34% for physical abuse, and 15% for neglect. Thirteen children were hospitalized. Children examined for sexual abuse had a mean age of 5.8 years and a median age of 5 years; 71% had normal findings on examination, including 48% of those with a history of penetration. Fourteen children were brought for evaluation on the basis of caretakers' misinterpretation, overconcern, or malice. The current spectrum of patients seen for child abuse or neglect reflects increased public and professional awareness of the problem. Earlier recognition of abuse, especially greater readiness to consider sexual abuse, brings younger, less physically injured children to the clinic.

(AJDC 1988:142:664-667)

The evaluation and treatment of abused and neglected children presents a challenging task for pediatricians. We report on aspects of our experience with abused and neglected children from 1984 to 1986 in an outpatient clinic. We emphasize that today's spectrum of abuse differs from that reported in the past decade: more children are being brought for evaluation, sexual abuse is the most frequent complaint and most often inpreschoolers, and volves clinically subtle abuse is being seen. Our clinical practice has changed in response, with less frequent hospitalization and more comprehensive outpatient diagnosis and treatment.

Our goal in this article is to document a representative sample of our current practice in the management of pediatric child abuse and to place these data in the context of growing public and professional awareness. As

with other medical conditions (ie, near-sudden infant death syndrome, Reye's syndrome) that have become increasingly familiar to pediatricians, our perceptions of child abuse, especially sexual abuse of children, have undergone evolution. A wider range of patients is identified, including those with less severe ("subclinical") injury. Parents and others may mistakenly perceive signs of abuse after hearing or reading about sexual abuse of children and bring their nonabused child for evaluation. "Classic" cases of multiple fractures, severely underweight children, and traumatic sexual assault now represent a minority of evaluations.

The benefits to children of increased societal awareness of child abuse are great. Knowledge of the current spectrum of child abuse and neglect will aid practitioners in caring for these children.

PATIENTS AND METHODS

Kino Community Hospital Pediatric Clinic, Tucson, a University of Arizona Department of Pediatrics affiliate, serves a primarily indigent, urban population in Tucson and Pima County, Arizona, a metropolitan area of nearly 600 000 people. Approximately 23 000 pediatric visits are recorded annually in the county-owned clinic; the clinic serves as a primary teaching site for University of Arizona pediatric residents and medical students. The clinic is one of the two referral sites utilized by Child Protective Services, Tucson. In this study, there was no systematic division of referrals by socioeconomic status or type of abuse. During the last year of the study period (no previous data are available), over one third of referrals in Pima County came to our clinic. The physicians care for patients through 18 years of age; however, some older teenagers, including victims of sexual assault, may occasionally be seen primarily by gynecologists or emergency physicians. If pediatric consultation was not requested, these patients were not included in this study. Children who were hospitalized were admitted to University of Arizona Medical Center, Tucson.

Data on ethnic origin of patients in this study are not recorded. Pima County statistics (1985) show the population to be 90.0% white, 2.9% black, 2.7% American Indian, 1.5% Asian, and 3.0% other; 20.5% of the population have Spanish surnames. Our clinic is located in an area with a high concentration of Mexican-Americans: 28% of our study group have Spanish surnames.

An ongoing log of child abuse evaluations was kept by the pediatric social worker during the study period (Jan 1, 1984, through June 30, 1986). All patients referred by Child Protective Services, the police or sheriff, or other agencies for evaluation of child abuse or neglect were included. In addition, any patient suspected of being abused or neglected was reported to Child Protective Services and logged. Emergency room records were reviewed by pediatric attending physicians on the following weekday to ensure that children examined there were appropriately evaluated and recorded. Two patients were added to the 380 in the log by crosschecking with admission records.

Complete physical examinations were usually performed in all types of abuse; if the evaluation was done primarily by a resident, the attending pediatrician confirmed the genital examination or positive physical findings in most cases. Colposcopic examination was not performed in sexual abuse cases. Laboratory and radiological studies were performed as appropriate. When transmission of venereal disease was thought possible, serologic tests for syphilis and cultures to isolate gonococci from three sites were obtained; microscopic examinations for Trichomonas or sperm were performed, if indicated. Cultures for Chlamydia were done routinely in 1986 and intermittently before then.

The patients were classified according to the most acute form of abuse found or suspected. A victim of sexual assault with physical trauma was classified under sexual abuse; a battered, underweight infant was categorized under physical abuse; and a child with physical injuries due to neglect was categorized under neglect.

RESULTS

Three hundred eighty-two evaluations were performed in the 30-month study period. Two hundred two children were referred by law enforcement or social service agencies (usually Child Protective Services). One

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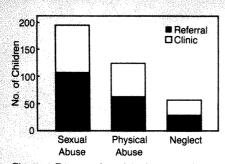


Fig 1.—Reason for visit (sexual abuse, physical abuse, or neglect) and source (referral by social agency or clinic-generated report).

| Table | e 1.—Hospitali Suspected Ab | |
|---------------|--------------------------------|---------------------|
| | No. of F | Patients |
| Type of Abuse | Hospitalized | Not Hospitalized |
| Sexual | 0 | 195 |
| Physical | 7 | 121 |
| Neglect | 6 | 53 |

hundred eighty children came with parents, other caretakers, or by themselves; they were then reported to the appropriate agency. Most nonreferred children evaluated for sexual abuse came with abuse identified as the chief complaint (71 [82%] of 87 children); self-identification of abuse by the child or family was less common in the patients with physical abuse (25 [39%] of 64 children).

One hundred ninety-five evaluations (51%) were completed for suspected sexual abuse, 128 (34%) for physical abuse, and 59 (15%) for neglect (Fig 1). The ratios of the referral patients (53% sexual, 32% physical, 15% neglect) were similar to those spontaneously presenting to the clinic (48% sexual, 36% physical, 16% neglect).

Girls predominated in our series of abused and neglected children; overall, 244 (64%) of 382 children were girls (Fig 2). The vast majority of sexually abused children were girls (164 [84%] of 195 children). Girls were most commonly seen for sexual abuse; boys were usually evaluated for physical abuse. Boys accounted for 57% of the children seen for physical abuse and 58% of the children seen for neglect.

Young children (birth through age 4 years) accounted for half of the children seen for sexual abuse and the

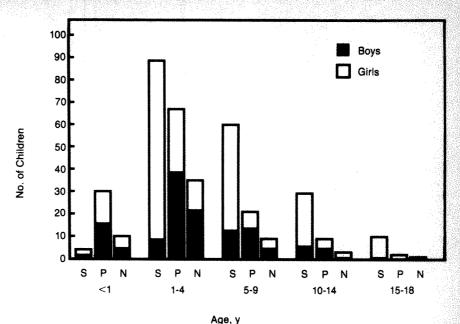


Fig 2.—Age and sex of children seen for sexual abuse (S), physical abuse (P), and neglect (N).

| | ble 2.—Venereal Disease in Sexual Abuse Evaluations | |
|---------------------|--|--|
| Venereal Disease | No. of Patients | |
| Gonorrhea | 3* | |
| Trichomonas | 1 | |
| Chlamydia (rectal) | 1 | |
| Venereal warts | 2 | |
| Total | 7 | |

*Cultures were positive from the throat, vagina, and rectum in one patient; the throat only in one patient; and the vagina and rectum in one patient.

great majority of children seen for physical abuse and neglect (Fig 2). Relatively more children over age 4 years (99 [51%] of 195 children) were examined because of sexual abuse than for either physical abuse or neglect. Children 4 years of age or younger accounted for 75% of the physical abuse category and 78% of the neglect category. There was no association (χ^2) between younger age (4 years or younger) and origin of the patient (patient referred from an outside agency vs patients who came without a referral) in sexual abuse cases (52 of 108 vs 44 of 87 cases). The sexual abuse group had a mean age of 5.8 years and a median age of 5 years; corresponding values were a mean age of 3.3 years and a median age of 2 years for the physical abuse group and a mean age of 3.1 years and a median age of 2 years for the neglect group.

Hospitalization was required occa-

| Table 3 | Listani al | Constrat | |
|-------------|------------------|-------------------------|---|
| IBDIE 3 | —History of | Mar 2 1 1 2 1 1 2 2 1 1 | OH VS |
| | | | |
| Absorber | at Cumminanti | بمحلم الرسم | |
| Abnorma | al Examinati | 6 8 18 mm - (6 16) | |
| | | | |
| Cindinae is | Coursel Abs | one Comb | |
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| | Lab | nination/ oratory dings |
|--|--------|-------------------------------|
| History | Normal | Abnormal |
| Unknown or no penetration Possible | 105 | 24 |
| penetration | 31 | 33 |

*Two patients did not undergo examinations and are excluded. $\chi^2 = 22.27$, P < .01.

sionally for evaluation and treatment of victims of physical abuse (fractures of the femur, retinal hemorrhages, intracranial hemorrhage, fracture of the skull, and burns were the major diagnoses) or neglect (failure to thrive, asthma, injury after inadequate supervision) (Table 1). No victims of sexual abuse, including rape, required inpatient care.

Seven children (4%) suspected of being sexually abused had venereal disease, as shown in Table 2, including two children evaluated for venereal warts. One hundred thirty-six (71%) of the 195 children evaluated had completely normal physical examination findings and no other evidence of abuse as determined from laboratory data. A history of penetration was associated (P<.01, χ^2 = 22.27) with abnormal findings (Table 3); 48% of those

giving a history consistent with penetration had normal results. Clinic-generated patients had more positive findings (32 of 87 findings) than did referral patients (25 of 107 findings); the association was significant $(P<.05, \chi^2=4.40)$.

A specific perpetrator was alleged in 160 of the sexual abuse evaluations; 101 (63%) were family or household members, 42 (26%) were other persons known to the child, six (4%) were daycare workers, and 11 (6%) were strangers. In 31 instances, the victim and caretakers did not describe the alleged abuser; the medical record gave inadequate information in four evaluations.

We reviewed our log to identify patients who had a low degree of suspicion by history, coupled with normal physical findings and laboratory data and no abnormal follow-up reports. In 14 instances, the children were referred to us for examination because of dirty or inappropriate living conditions. Social problems (a family of five children living in a car, children being raised by drug abusers or prostitutes) presented to the medical care system in this way. In four other patients, examination was performed at Child Protective Services' request because of inappropriate parental behavior, although the behavior was not specifically abusive or neglectful; these instances may reflect the intuition of the protective services worker when other investigation of a family yields normal findings.

Five children (four agency referrals, one clinic patient) were referred as a result of alleged malicious or false reporting. Three of these patients involved accusations by adults of sexual abuse in the setting of marital, extended family, or neighborhood disputes; another involved a teenager who alleged physical abuse by an adult in the home. The fifth patient was a 2-year-old boy who reported "I was raped. Why me?"; his mother had psychiatric illness and had undoubtedly coached the child.

Misinterpretation of physical findings by parents or other caretakers and overconcern about sexual abuse may lead to a clinic visit. Nine victims (five clinic generated, four referrals) of possible sexual abuse fit this category. All had normal examination findings, although initial complaints in-

cluded a "red," "enlarged," "swollen," or "foul-smelling" genital area. Other children presented with nonspecific behavioral symptoms that seemed not to be manifestations of hidden abuse; rather, maternal psychiatric illness or anxiety secondary to the mother's childhood molestation appeared to have linked the symptoms with possible abuse.

COMMENT

Our series of patients represents the spectrum of child abuse in the mid-1980s; these patients were seen in a social milieu much more aware of abuse, especially sexual abuse, than that of a decade ago. As recognition and awareness have changed, so have the kinds of patients presenting to us.

Sexual abuse is now the predominant form of abuse or neglect evaluated in our clinic; this is a dramatic change since Kempe¹ emphasized sexual misuse of children as a hidden problem in 1977. Nationally, American Humane Association, Denver, data of abuse and neglect reports, obtained from diverse sources (eg, only 11% of such reports came from physicians in 19812), showed that 6.5% concerned sexual abuse in the late 1970s,3 7% in 1981,2 and 13% in 1984.4 Krugman4 reported that 27% of Colorado reports in 1984 were for sexual abuse; Jason et als reported that 17% of Georgia's confirmed cases in 1975 through 1979 were in the category of sexual abuse. Many children, especially neglected ones, are not taken immediately to physicians' offices for evaluation, so that clinic data will naturally differ from reports to agencies. The trend, however, is clear, and one third of child abuse evaluations were done for sexual abuse in Children's Hospital in Winnipeg, Canada, in 1981 through 1983.6

Girls were victims more commonly (64%) than boys in our series because girls accounted for 84% of visits for sexual abuse. Whether one sex or the other is subjected to more mistreatment (considering all forms) in our culture cannot be ascertained from our data, but we suspect that girls are in the majority.

The median and mean ages of children seen for sexual abuse at our clinic were 5 and 5.8 years, respectively; sexual misuse of young children is increasingly reported. Pediatric se-

ries, ours included, are likely biased against counting older adolescents, even though review of emergency room records does not reveal large numbers of "missed" cases at our hospital. Three large series of sexual abuse in children from the late 1970s reported mean ages of 9.2 years, 10.5 years for girls and 8.7 years for boys,8 and 11.3 years.9 Hunter et al10 reported an average age of 9 years in children seen for sexual abuse in 1972 through 1979; the abuse had frequently gone on for two to three years previously. They hypothesized that "prior reviews have concentrated on more readily identifiable cases," with a mean age of 11 years. Our report extends hypothesis-even this younger children are encountered today. Abuse is less hidden, and identification by parents, child care workers, and medical professionals occurs earlier in the course of long-term abuse. More weight is given to verbal and nonverbal clues that indicate sexual abuse in young children.

Physical examination yielded abnormal findings (including erythema, abrasions, lacerations, edema, bleeding, enlarged introitus, and decreased anal tone) for 29% of sexual abuse victims in our group; 3.6% had venereal disease, with 1.6% having gonorrhea. These percentages identify a lower disease and trauma burden than in some past series. Rimsza and Niggemann⁷ found a 7.4% incidence of gonorrhea in their patients; 77% had abnormal physical findings. Tilelli et al⁹ noted a 2.3% incidence of gonorrhea and a 30% incidence of abnormal physical findings The study of Dejong and colleagues,3 also conducted in the late 1970s, had corresponding figures of 3.1% and 22%, respectively. White et al" reported a 13% incidence of venereal disease during a study period from 1976 to 1980.

The children in our study were younger than in other series and, hence, were less likely to exhibit aknormal findings on examination; "indecent liberties" rather than "rape" or "aggravated rape" more commonly occur in younger age groups. In addition, earlier recognition may have prevented progression to more invasive abuse. Other current factors, however, would tend to increase the percen-

tages of abnormal findings: more subtle findings (enlarged introitus, ^{12,13} perianal hyperpigmentation, ¹⁴ scars of hymen or posterior forchette¹⁵) are being recognized, although their significance is still unclear, ¹⁵ and methods for *Chlamydia* testing are now more readily available. Sarles¹⁶ discussed underreporting of sexual abuse in 1982, saying that only "the tip of the iceberg" was being seen; the rest of the iceberg is now becoming visible.

The lack of abnormal physical or laboratory findings in 70% of our sexual abuse evaluations, including 48% of those giving a history of penetration, is stressful for patients and families. Most children had a definite history of abuse, although few were violently assaulted. Families and victims, as well as protective service workers and the courts, must understand that normal findings do not rule out abuse. "Penetration" to the child may mean interlabial, not intravaginal, touching; those children who reported penetration yet whose physical examinations yielded normal results can be believed. 17 Summit 18 described the tendency of these vulnerable children to retract the truth of their sexual assault in the face of pressure by disbelieving family members and professionals; physicians and pediatric social workers must educate involved parties in instances of children whose examination results are normal. Families and children must be reassured

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that no physical damage or disease resulted from any abuse; however, the more common and serious emotional consequences of abuse must be faced.

Pediatricians, pediatric residents, and pediatric nurses accustomed to dealing with tangible physical and laboratory findings in abused children also find the normality of most sexual abuse evaluations difficult to accept. The reluctance of pediatric residents to perform genital examinations in girls has been documented.19 Without experience with the routine examination, there is apprehension about differentiating normal from abnormal results, especially when later court testimony is possible. Ladson et al²⁰ have shown that many practicing pediatricians should indeed be apprehensive: genital anatomic landmarks and abnormalities were not recognized by pediatricians in their report. Seeing many abused girls with normal findings increases the examiner's selfdoubt and raises questions about the utility of the examinations or cultures.

Normal examination findings occur when children have not been abused. Some children came to our clinic because worried caretakers misinterpreted behavioral or physical signs; an analogy may be made to mongolian spots or car seat burns as "ringers" for physical abuse.^{21,22}

Fabricated stories of abuse are uncommon²⁸; they occurred in five of our 382 children. The setting of the

alleged abuse amid a custody or other dispute, accounts by the child that reflect adult perceptions and language rather than a child's, and inconsistent interviews may be clues. Physicians must remember that on-the-spot judgments in these situations are not wise; subsequent denial of abuse could be recantation of a true story brought by family pressure. 4.18

The great majority of children in our study were not hospitalized. The new spectrum of child abuse requires less acute medical intervention. Helfer and Kempe²⁵ mandated hospitalization for all abused preschoolers in their classic 1972 text; alternatives to hospitalization are now available and usually more desirable. Increasing numbers of child abuse reports, combined with growing concern about hospitalization costs, have led to the establishment of improved systems of outpatient evaluation. A coordinated approach, allowing simultaneous interview with physicians, social workers, and child protective service workers, is ideal in sexual abuse evaluations. In children who fail to thrive socially, outpatient evaluation over time is far superior to acute evaluation in the hospital and may be more cost-effective.26

Planning for child health care services and pediatric education must take into account the new spectrum of abuse we have described.

We thank A. Binkiewicz, MD, G. Duncan, MSN, and M. Raddish, MD, for valuable suggestions.

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Educational Interventions

Hugh D. Allen, MD, Tucson Fredric Burg, MD, Philadelphia Harold Levine, MPA, Galveston, Tex Barbara Starfield, MD, Baltimore Larrie W. Greenberg, MD, Washington, DC

> Purpose. - This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

> Editorial Comment.-What is discipline and what is abuse? This study evaluated not only resident perceptions of the question but also residents from different specialties for similarities and differences. Suggestions are made for a more systematic approach in overall resident education. Does this apply to your program?

What Residents Know About Child Abuse

Implications of a Survey of Knowledge and Attitudes

Alan Woolf, MD, MPH; Leslie Taylor, MD; Lora Melnicoe, MD, MPH; Kathy Andolsek, MD, MPH; Howard Dubowitz, MD; Edward De Vos, EdD; Eli Newberger, MD

 Residency training programs are the appropriate milleu in which physiclans should receive specialized training in the diagnosis and management of child abuse. The purposes of the present study were to assess and compare residents' knowledge of child abuse and their attitudes toward the propriety of different forms of childhood discipline. We surveyed 192 residents from seven different training programs with questionnaires probing their knowledge of child abuse and their attitudes toward childhood disciplinary measures; 161 (84%) of the questionnaires were satisfactorily completed by residents in pediatrics (n = 87), family medicine (n = 51), and surgery (n = 23). Both pediatric res-

idents and family medicine residents outperformed surgery residents in one subscale and the total score on the test. Scores were not related to year of training or attitudes toward childhood discipline but were correlated with self-reports of previous child abuse teaching. Residents' performance on a childhood disciplinary measure demonstrated wide latitude in their rating of the acceptability of 23 different modes of childhood discipline. Our findings indicate a need for a more systematic approach to residents' education in childhood intentional injuries and some value clarification of their attitudes toward various forms of childhood discipline.

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Child abuse continues to be an important cause of death and disability among infants, children, and adolescents in the United States. It is a major public health issue due not only to the sheer volume of intensive medical and social services utilized by its victims but also to the associated long-term physical and psychosocial disability and suffering. Since Caffey's¹ original clinical and radiologic descriptions of child abuse syndrome in the 1940s, the medical profession has rightfully asserted its responsibility, authority, and expertise in the diagnosis and management of such cases. Suspected child abuse and neglect continue, however, to be underreported health problems in the United States.2,8 Medical educators have suggested that residency teaching programs are the appropriate milieu in which to train physicians in the diagnosis of child abuse and the management techniques crucial to the proper disposition of child abuse cases.4,5

In this study, we surveyed a cross section of pediatric, surgical, and family medicine residents to determine their attitudes toward childhood discipline and their knowledge of the diagnosis and management of child abuse. We were interested in the correlation of knowledge and attitudes with previous education and experience with child abuse cases, subspecialty field, and level of training. Our purpose was to better understand whether residency programs are fulfilling their mandate of instructing residents about child abuse and how such instruction might be enhanced.

MATERIALS AND METHODS

Two questionnaires were used to assess the knowledge and attitudes of physicians toward childhood inflicted injuries.

Knowledge Questionnaire

A 75-item multiple-choice questionnaire was created to cover the domains of knowledge thought relevant to the diagnosis and management of child abuse. Questions pertaining to epidemiology; diagnostic symptoms, signs, and mechanisms of injury: differential diagnosis; and legal aspects of abuse were formulated based on information from medical texts and journals. The questions were designed to probe information residents might reasonably be expected to have acquired in the area of child abuse. The questionnaire was piloted on 20 experts in the field to ensure clarity and appropriate content. Based on the suggestions and recommendations of this expert panel, ambiguous or overly difficult questions were discarded. The revised 50-item questionnaire included nine questions on epidemiology, 28 on diagnosis, eight on differential diagnosis, and five on legal aspects of child abuse.

Attitudes Questionnaire

To assess residents' views on childhood discipline, the disciplinary attitudes questionnaire reported originally by Morris et ale was given. Twenty-three different methods of discipline were rated by subjects as being either an "acceptable," "not acceptable," or "reportable" means of punishment for a 5-year-old child.

House staff were recruited into the study during the final three months of their internship or residency year. All residents in specific subspecialties from six separate institutions were sampled: The Children's Hospital, Boston (Pediatrics); Duke University, Durham, NC (Family Medicine); University of Massachusetts, Worcester (Pediatrics and Family Medicine); Beth Israel Hospital, Boston (Surgery); Marshall University, WVa (Pediatrics); and University of Maryland, Baltimore (Pediatrics). House staff were asked to complete a short, demographic questionnaire and were then given both the medical knowledge and attitudes questionnaires to complete. The test was untimed and completed without proctoring. Residents were asked not to look up answers or to share their information with colleagues.

| Demographic Characteristics of House Staff Sample | | | | |
|---|--------------------------------|---------------------|--------------------------------|-------------------|
| | % of Residents by Subspecialty | | | |
| | Pediatrics (n = 87) | Surgery (n = 23) | Family Medicine (n = 51) | Total (N = 161 |
| Sex | - | | | |
| М | 47 | 70 | 49 | 51 |
| F | 53 | 30 | 51 | 49 |
| Race | | | | |
| W | 89 | 87 | 100 | 92 |
| В | 5 | 0 | 0 | 2 |
| Other | 8 | 13 | 0 | 6 |
| Marital status | | | | |
| Single | 40 | 70 | 31 | 42 |
| Married | 60 | 26 | 67 | 57 |
| Divorced or separated | 0 | 4 | 2 | 1 |
| Children | | | | |
| Yes | 23 | 4 | 28 | 22 |
| No | 77 | 96 | 72 | 78 |
| Year of training | | | | |
| First | 26 | 26 | 31 | 28 |
| Second | 31 | 17 | 29 | 29 |
| Third | 40 | 35 | 39 | 39 |
| Fourth or greater | 3 | 22 | 0 | 4 |
| | | | | |

29.1

79

29.0

83

Statistical Methods

Age, y

Group response rate

Internal consistency of test scales was determined by successively analyzing Cronbach's coefficient a. The internal consistency of test items was such that the refined total of 28 individual items reached Cronbach's coefficient $\alpha = .71$. These 28 questions were used to investigate group differences, correlations, and all subsequent statistical comparisons. Duncan's Multiple Range Test was used to test for significant pairwise differences between resident subspecialty groups when a significant overall F statistic was obtained. For dichotomous variables, associations with group membership were evaluated using the χ^2 statistic. The probability of a type I error was set at the .05 level for consideration of statistical significance. The Spearman rank correlation was used to investigate the relationship between total knowledge score and year of training. previous instruction about child abuse, and attitudes toward childhood discipline.

RESULTS

One hundred ninety-two questionnaires (available from Dr Woolf on request) were distributed and 161 were satisfactorily completed for a response rate of 84%. Response rates from individual institutions varied from 79% to 88%. The completed questionnaires from 87 pediatric residents, 51 family medicine residents, and 23 surgical residents are included in the analysis.

29.4

88

29 2

Demographics

The Table shows the demographics of the sample. The house staff sample was 92% white and 51% male. About 50% were married, although this varied greatly according to subspecialty, with 74% of surgeons either single or separated. Twenty-two percent of the residents were parents, although this varied by subspecialty, with only 4% of surgical house staff reporting they had children. The house staff responders were evenly represented with respect to year of training: 28% were in their first year, 29% were in their second year, and 43% were in the third year or higher. There were no differences between residency groups with respect to age (mean age, 29 years).

Previous Training on Child Abuse

Figure 1 summarizes the total hours of exposure to didactic lectures on child abuse reported by the residents in the three subspecialties. Between one and four hours was the modal level of instruction for all subspecialties. No family medicine resident reported "no

instruction," and no surgery resident reported more than nine hours of instruction. Surgeons reported fewer hours of instruction in child abuse topics (29% indicated five hours or more of instruction) than pediatricians (58% indicated five hours or more of instruction) or family medicine residents (47% indicated five hours or more of instruction). Sixteen percent of pediatric residents and 8% of family medicine residents reported that they had received more than 15 hours of instruction about child abuse in their training. Neither surgery nor family medicine residents had ever been in court to testify concerning a child abuse case. By contrast, 22% of pediatric residents had made one or more court appearances to testify on behalf of a maltreated child.

Medical Knowledge of Child Abuse

Medical knowledge scores by subscore and total score are shown in Fig 2. Residents demonstrated a mean total score of 66% on the unreduceditem pool that measured knowledge of child abuse and achieved 83% correct answers on the 28 selected questions, with high internal consistency in regard to the four domains of knowledge tested. Significant differences in residency performance by subspecialty were noted. Pediatric and family medicine residents outperformed surgery residents in the epidemiology subscale of the knowledge questionnaire and consequently in the total score for the test. While both family medicine and pediatric residents also had higher mean scores than surgery residents in the diagnosis, differential diagnosis. and law subscales, these differences represented trends that did not reach statistical significance. There were no appreciable differences in any of the scores between pediatric and family medicine residents. When the data were analyzed by sex, however, female residents outperformed male residents in most of the subscales: epidemiology (F[1,149] = 7.64, P = .006),law (F[1,149] = 10.92, P = .001), and total score (F[1,149] = 5.99, P = .016). With the data stratified by sex, female family medicine and pediatric residents still showed a trend toward better scores than female surgery resi-

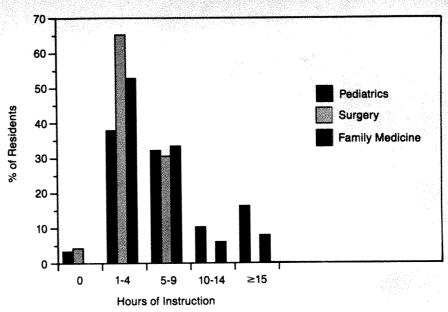


Fig 1.—Total reported hours of child abuse instruction.

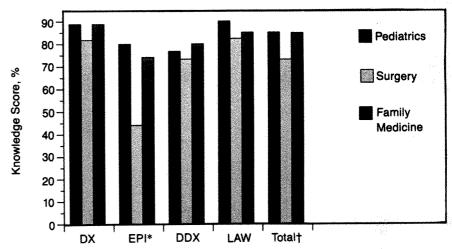


Fig 2.—Resident knowledge by subscale and subspecialty DX indicates diagnosis; EPI, epidemiology; DDX, differential diagnosis; and LAW, legal. Asterisk indicates F(2,149) = 16.56, P = .0001; dagger, F(2,149) = 5.13, P = .007.

dents on the test; however, these differences did not reach statistical significance.

Childhood Disciplinary Attitudes

There were no significant mean differences in total scores among residency groups in describing which of 23 different disciplinary measures used on a 5-year-old child are acceptable, nonacceptable but not reportable, or reportable as child abuse. There was, however, considerable variation among residents as to which individual punishments are reportable as child abuse. Figure 3 presents eight of the more variably scored disciplinary types of the 23 total. Eleven

percent of all residency groups felt that locking a child in a room for one hour is reportable. Eight percent of family medicine residents felt that spanking a child with a belt is reportable, contrasted with 23% of surgery residents and 26% of pediatric residents. Forty-eight percent to 58% of the three groups felt that spanking with a belt so as to leave a red mark is reportable; this percentage increased to between 79% and 90% if the belt left a bruise. Thirty-three percent of pediatric residents indicated that they would report an incident in which a child was slapped in the face as punishment, compared with only 28% of surgery and 20% of

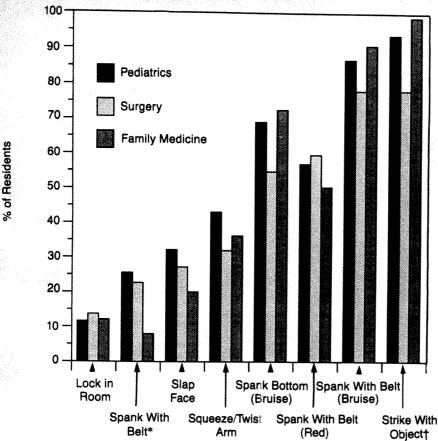


Fig 3.—Reportability of childhood disciplinary measures. Asterisk indicates $\chi^2 = 6.35$, P = .040; dagger, $\chi^2 = 9.46$, P = .009.

family medicine residents. Forty-three percent of pediatric residents felt that squeezing or twisting a 5-year-old child's arm so as to produce pain was a reportable punishment, contrasted with only one third of surgery and family medicine residents. Over 50% of all three groups thought that a child whose bottom had been spanked so as to leave a bruise was a victim of abuse. However, 93% of pediatric residents and 98% of family medicine residents but only 78% of surgery residents considered as reportable an incident in which a child was struck with an object that left a bruise.

Correlations Between Knowledge, Attitudes and Instruction

There were no apparent correlations between the extent of knowledge about childhood inflicted injuries and years of training (r=-.04) or attitudes toward punishment as expressed as the aggregated total number of punishments considered reportable as abuse (r=.04). There was a significant positive correlation, however, as shown in Fig 4, between

the resident's reported exposure to child abuse instruction in the training program and his or her score on the medical knowledge examination (r=.24, P=.005).

COMMENT

It is well established that misdiagnosis and a lack of early intervention and remediation in cases of abuse may culminate in the later death of the child or in adverse long-term consequences, including subsequent injury, for the child and his or her family. All 50 states now have child abuse reporting statutes, and social services agencies are mandated to investigate each reported case. The number of reports of abuse has risen exponentially in the past ten to 15 years since these statutes were passed.

The failure of physicians to report suspected cases of child abuse was described as early as 1963 by Bain.⁷ He theorized that physicians might not report a case of childhood inflicted injury for a number of reasons (eg, misdiagnosis, denial, ignorance of the reporting process, nonconfrontational

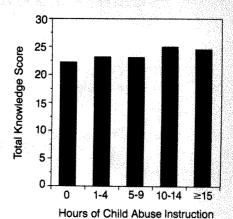


Fig 4.—Resident knowledge and hours of instruction.

style, or anxiety about the physician's own community standing).

More recently, there has been discussion of health care providers' resistance to dealing with child abuse cases. Silver et als suggest that physicians' failure to consider the diagnosis, at least in some cases, relates to their subjective feelings about child punishment and their own misperceptions about their role and responsibilities according to child abuse reporting statutes. Morris et als studied physicians' knowledge and attitudes and suggested that it is now unlikely that physicians are ignorant of the law but are more likely to underreport because of their own values and attitudes toward abuse. Seventy percent of their sample of 58 family practitioners and pediatricians in private practice had not reported a single case in the previous year. The authors speculate that younger physicians were more willing to report because of child abuse training required in medical schools and residency programs. In a survey of 1367 physicians, Chang et al9 found discrepancies between physicians' attitudes about what should be reported and what was usually reported. Solomons¹⁰ reviewed 161 cases of fractures, burns, head trauma, and contusion seen in the emergency clinics by interns and residents and concluded that 60% of the charts did not contain adequate information to determine whether the diagnosis of child abuse was even considered. Orr11 found similar medical record deficiencies in resident evaluations of sexually abused children. Snyder and Newberger¹² have recently reported gender, training year, and

specialty differences in how hospital professionals rate the seriousness of child maltreatment cases.

The results of our study suggest room for improvement in the knowledge base of pediatric, family medicine, and particularly surgery residents in the epidemiology, differential diagnosis, diagnostic, and legal aspects of child abuse. The mean total raw score of 66% suggests deficiencies in the understanding of the principles of diagnosis and management of these cases. Our study showed no accumulation of knowledge during residency training; first-year residents did about as well as those in their second or third year of training. A more encouraging result was that formal instruction in child abuse did seem to make a difference. Those residents who reported more exposure to formal child abuse training also performed better on the knowledge questionnaire. A limitation of this study is that we did not investigate the various child abuse curricula available in the different teaching programs and instead relied on the residents' reports as a proxy indicator of the existence and success of such curricula. Just how and where residents acquire their knowledge about childhood inflicted injuries and what might be the most efficient teaching mechanism to transmit such knowledge remain unclear. The number of residents we sampled in each subspecialty is small compared with the universe of physicians in training; our results must therefore be interpreted with caution when considering their generalizability.

Despite general agreement in the residents' perceptions of the acceptability of different methods of childhood discipline, we discovered some alarming exceptions that could result in both overreporting and underreporting. Five percent to 10% of residents in all three subspecialties found that, while unacceptable, striking a child with a belt and leaving a mark would not be reportable as abuse. Conversely, some residents stated that they would consider punishments such as sending a child to his or her room without supper or locking a child in a room for less than an hour as reportable. While there is certainly a considerable degree of latitude as to opinions and judgment with respect to childhood punishment, our results suggest that residents' attitudes need to be clarified. These influences, along with contextual cues of the case and the residents' assessments of the family as a whole, influence their decision making in considering the appropriateness of a type of punishment administered to a child and its consequences. Whether such decisions, perhaps formulated in the context of a resident's own upbringing, culture, religion, or background, can be influenced within a training program requires further study.

We do not infer that residents' responses to medical knowledge and attitude questionnaires necessarily reflect their professional demeanor or competency when they are actually confronted with a child abuse case in the emergency clinic or on the wards. Previous studies have demonstrated that physician performance on clinical vignettes in a test situation may not correlate well with their actual practice style and decision making in the clinical situation.¹³

However, we feel that these are important core principles for the physician to carry into the clinical setting. Our results indicate a need for a more systematic approach to the education of pediatric, surgery, and family medicine residents regarding childhood inflicted injuries. Such training may take many forms, eg, clinical case conferences, didactics, case management studies, and clinical experience. Pediatricians and family medicine residents probably have more opportunity than surgeons to manage child abuse cases; clinical experiences must be closely linked to and enhanced by formal instructional methods. Other studies are needed to define the knowledge base of medical students in childhood inflicted injuries; perhaps more teaching efforts are needed here. Further investigation is also needed to determine whether or not the knowledge of and attitudes toward childhood inflicted injuries change after residency training. This might better dictate the needs of the practicing physician for continuing medical education in this

Both knowledge about child abuse and attitudes concerning acceptable

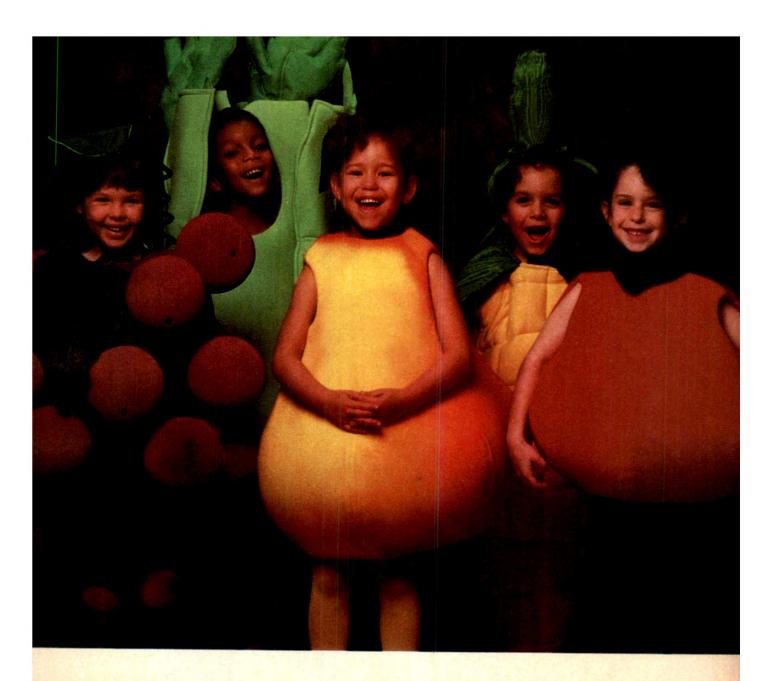
discipline for young children may influence the resident's decision making when confronted with children who are injured. Formal curricular attention to both of these areas in child abuse instruction may help the resident to become a more informed professional and facilitate the management of these difficult and complex cases. Only through continued monitoring of our efforts can we improve the quality of our teaching about child abuse to this new generation of physicians and thereby improve the quality of care the patients and their families receive.

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Gastrointestinal System: Epigastric distress, anorexia, nau-sea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

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PhDs in Pediatric Departments

M. Patricia Leuschen, PhD; Robert M. Nelson, Jr. MD; Jaime L. Frias, MD

 A survey on PhDs in academic pediatric departments was sent to members of the Association of Medical School Pediatric Department Chairmen (70% responded). Significant numbers (14.5%) of pediatric faculty members hold PhDs. Another 3.6% hold PhDs/ MDs. Research is their major responsibility in every subspecialty except psychology. The majority of PhDs (51%) are assistant professors (8% tenured) in contrast to 37% of MD faculty (14% tenured). The majority of PhDs at full professor (56%) are tenured compared with only 44% of MDs. Separate criteria exist for promotion for PhDs in 42% of departments. For promotion to associate professor, the mean number of refereed publications is 18 (median, 15); for full professor, the number ranges from ten to 50 (median, 40). Extramural research funding carries the highest weight in evaluating research efforts. PhDs could impact significantly on long-range planning in academic pediatric departments. (AJDC 1988;142:675-678)

In the last decade the structure of pediatric departments in academic institutions has changed dramatically due principally to the growth of subspecialties. One factor in specialization that has not received much atten-

For editorial comment see pp 598 and 599.

tion is the presence of faculty with doctoral degrees other than physicians. This survey is an attempt to look at this segment of the faculty to evaluate their overall distribution and role in academic pediatrics.

METHODS

A survey questionnaire was constructed to collect information on the number of faculty who hold PhDs, their academic rank and subspecialty affiliations, salary level, and criteria for promotion. All items were

closed questions although room was included for comments. The survey was mailed to all members of the Association of Medical School Pediatric Department Chairmen Inc, University Affiliation Roster for 1986 in the United States. The first mailing included a self-addressed return envelope and was followed up six weeks later with a second mailing to those institutions that had not responded.

All information was coded by institution

All information was coded by institution and American Academy of Pediatrics district.² Departments were subdivided into large departments (>50 total faculty) and small departments (<50 total faculty). Data were collated by microcomputer using Powerbase and statistically analyzed using Abstat.

RESULTS

Of the 132 mailed surveys, 92 were returned for a response rate of 70%. The proportion of pediatric faculty who hold either PhD or MD/PhD degrees is illustrated in Fig 1. Of 3843 pediatric faculty, 557 (14.5%) hold a PhD and another 138 (3.6%) have combined PhD/MD degrees. The number of PhDs in individual departments varies substantially and ranges from zero to 54 (0% to 31%). The relative size of the department alone does not correlate well with the number of PhDs on the faculty (Fig 2). Large departments show the greatest variability. When geographic area and relative size are both analyzed, large departments along the Eastern Seaboard report few PhDs on their faculties (≤4%) while smaller departments in the same districts do not vary significantly from the mean (14.5%) (Fig 2). The highest percent of PhDs is found in large departments in California and in the central and midwestern states. The survey response rate varied with the geographic district. District 2 (New York State) had the lowest response rate (42%) while district 9 (California) had the highest (100%).

Fifty-one percent (237/469) of the PhDs hold the academic rank of assistant professor (Fig 3). In contrast, 37% (888/2372) of the MD faculty are assistant professors. Seven percent

(35/469) of the PhDs hold the rank of instructor compared with 14% (232/2372) of the MD faculty. Another 27% (126/469 PhDs and 651/2372 MDs) from both groups are associate professors. Fifteen percent (71/469) of the PhDs are full professors, while 22% (510/2372) of the MDs hold that rank.

There are similarities and differences in the percent of PhDs compared with MDs who hold tenure at specific academic ranks. Neither group had significant numbers of instructors who hold tenure. Only 8% of the PhDs hold tenure at the rank of assistant professor compared with 14% of the MDs. At the rank of associate professor, 36% of the PhDs are tenured compared with 39% of the MDs. For full professors, a higher percent of PhDs (56%) than MDs (44%) hold tenure.

Virtually all pediatric subspecialties have PhDs involved in both service and research roles (Fig 4). Fifty-two percent are full-time researchers while 40% spend more than 30% of their time on patient services. Full-time research is the major responsibility of PhDs in every subspecialty except psychology.

Only 75 of the 92 departments that responded completed the section on salaries (82% of respondents or 57% of the total possible). Sixty percent indicated that their MD faculty receive professional fees income in addition to a base salary. The salary of the PhDs averages between 70% and 83% of MDs within an equivalent rank depending on whether the MDs receive profes-

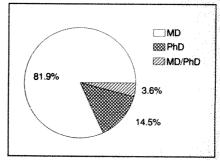


Fig 1.—Proportion of pediatric faculty who hold PhD, MD/PhD, or MD degrees.

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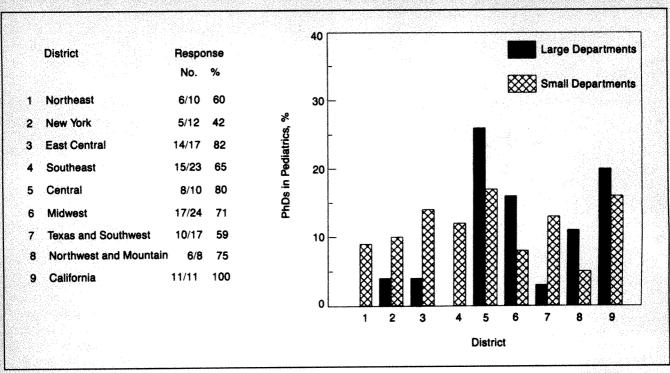


Fig 2.—Analysis of response using Academy of Pediatrics districts. Large departments contain more than 50 faculty.

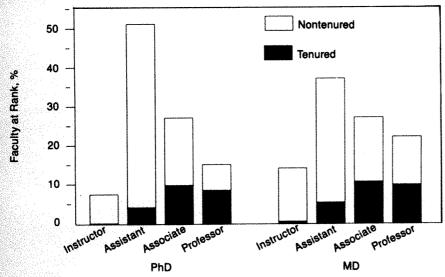


Fig 3.—Percent of faculty at each academic rank subgrouped by tenure status.

sional fee income.

Separate criteria for promotion of PhDs exist in 42% of the departments surveyed. A specific publication record is necessary for promotion in 58% of the responding departments. However, a third of the respondents indicated that quality is more important than quantity. For promotion to associate professor, the mean number of refereed publications is 18 (median, 15). For promotion to full professor, the number ranged from ten to 50 with

a mean of 26 and a median of 40.

In one section of the survey, respondents were asked to rank four criteria for evaluating research using a scale of 0 to 4. Extramural research funding carried the highest weight in evaluating research efforts toward promotion and tenure for PhDs (Fig 5). National presentations and service on editorial boards or National Institutes of Health (NIH) study sections carry more weight than teaching. Eighteen percent of the PhDs hold NIH funding

compared with 8% of the MDs. Figure 6 illustrates how well faculty (PhDs and MDs) meet specific promotion criteria. While the actual number of MDs meeting any specific criterion is higher, the percent of PhDs who meet the criteria is greater (Fig 6).

COMMENT

Although PHDs constitute a significant proportion of pediatric faculty in academic institutions, to our knowledge, there are virtually no published reports evaluating their role in these departments. In developing longrange plans for academic departments, the distribution of PhDs in patient service and research programs and their potential role should be evaluated. This survey provides information previously unavailable on a national level about the current demographics of PhDs in pediatric departments. These data should help in evaluating the role and impact of PhDs in clinical academic depart-

One of the few areas in which published data are available comparing MDs with "faculty with other doctoral degrees" is the American Association of Medical Colleges salary data.³ This indicates that when full-time pediatric

faculty in private and public US medical schools who receive only a base salary component are compared, PhDs receive from 62% to 66% of MD salaries. When base salary plus supplemented components are considered. the ratios are similar (64% at the level of assistant professor to 67% for full professors). Salary rates in this study are higher (70% to 83%) depending on

similar academic ranks receive sub-

rank and whether base salary alone is considered. Sampling methods and derivation of the data may account for the differences. The responding pediatric departments may reflect a selected population, interested in using PhDs and currently paying a higher than average salary ratio. In any case. the figures illustrate that PhDs at

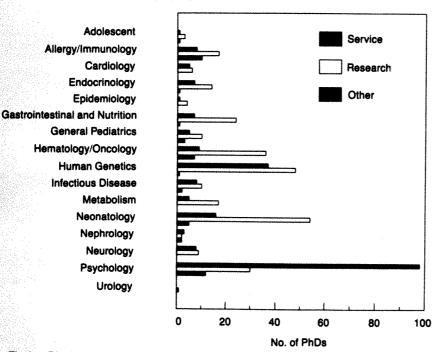


Fig 4.—Distribution of PhDs within subspecialties subgrouped by major responsibility.

stantially less salary compensation than MDs.

Large departments in district 9 (California) and district 5 (Michigan, Indiana, and Ohio) use the highest percent of PhDs. On the surface, one might assume that this is due to the clustering of strong basic science programs in these geographic areas or to less competition by qualified MDs or MD/PhDs. District 2 (New York State) is the district with the lowest survey response rate (42%) and their use of PhDs particularly in large departments is low (4%). When all districts along the Eastern Seaboard are analyzed, none of the large departments responding use significant numbers of PhDs (Fig 2). Small departments within the same areas use a significantly higher percentage of PhDs. It is not immediately apparent why large departments in these districts use fewer PhDs. Are the larger number of MDs in the larger departments allowing clinicians more time for academic research? The majority of MDs in these departments are at the lower academic ranks, and competition for advancement may be a potent stimulator of research. The answer is probably a complex one and needs further investigation.

While 42% of the departments indicate that they use separate criteria for

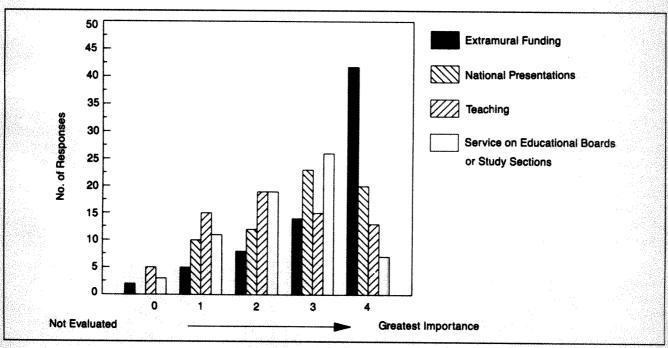


Fig 5.—Weight given specific criteria for promotion.

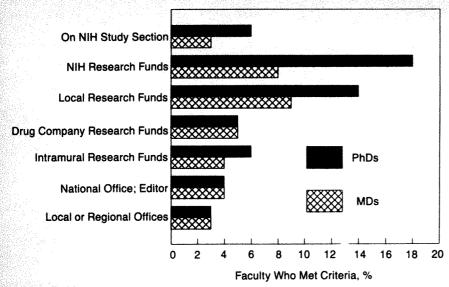


Fig 6.—Comparison of how well PhDs and MDs meet standard criteria for promotion. NIH indicates National Institutes of Health.

the promotion of PhDs, the emphasis seems to follow traditional guidelines. For example, a good publication record (quality not quantity) and extramural research funding are common criteria for promotion of PhDs in basic science departments. The survey indicates that this is also true for PhDs in pediatric departments. Teaching, while a primary function of all academic institutions, does not carry the same weight in evaluation of promotion, tenure, or both. Since PhDs in pediatric departments function primarily in either service or research capabilities, it is not surprising that teaching received a low rating as a criterion for promotion.

The traditional academic ranks (eg, assistant professor, full professor) are still used in most pediatric departments, but survey comments indicate that there is a substantial degree of flexibility within rank, ie, research assistant professor or clinical assistant professor. As in most studies, this survey brought up as many questions as it answered. Further evaluation of the use of subgroups within academic ranks and their role in setting criteria for promotion and tenure would be useful.

The effectiveness of nontenure tracks for either full-time research faculty (usually PhDs) or clinical faculty (usually MDs) is another issue that was not directly addressed. However, analysis of the data (Fig 3) on

tenure indicates two differences between PhDs and MDs that are of interest. First, the majority of PhDs are assistant professors and their tenure status is significantly lower than MDs at that same rank. Is this due to the age of the faculty (less time in rank for PhDs) or is it due to the use of nontenure track research lines for PhDs? For full professors, the tenure status is reversed. PhDs who are full professors are more likely to be tenured than MDs at the same rank. We can speculate that there are more MD clinical professors outside tenure tracks than PhDs. Or it could just be that more PhDs who have met the criteria for promotion to full professor (a good publication record, NIH funding, etc) have been rewarded with tenure.

Of all the pediatric subspecialties, psychology has the largest number of PhDs (Fig 4). While the majority work in service capacities, a significant number are involved in research. All other subspecialties have more PhDs involved in full-time research than service. It is this use of PhDs in research positions that adds a new direction to pediatric research and may play an important role in longterm departmental planning. In their 1983 study analyzing research associated with family medicine, Culpepper and Franke⁴ reported that common major impediments to research included lack of faculty time, lack of faculty funding, lack of research skill, and lack of role models. A working hypothesis is that pediatric research often meets with the same stumbling blocks. The increased use of faculty with doctorates other than MDs could help overcome some of these impediments. Research skills and an expertise in competing for national research funding are often a major emphasis in the training of PhDs. Such skills necessarily rank behind clinical training in the education of the MD. Collaborative research programs utilizing both MDs and PhDs would alleviate some of the problems associated with the limited time clinical faculty may have for day-to-day research, laboratory management, grant preparation, and administration as well as with the lack of highly specialized research skills. Or MDs can provide a clinical insight to applied research that cannot be obtained in any other way.

The nature of academics will cause pediatric departments to continue to recruit MDs with subspecialty training. Divisions, sections, or subgroups of clinical faculty with common interests are now commonplace. MDs will continue to make up the majority of pediatric faculty within these subgroups, particularly where clinical service is involved. However, technical research skills have also become complex and more specialized. When clinical service puts increasingly heavier time constraints on the development of research programs, alternative methods for administration and management of research become attractive. PhDs can play an important role in maximizing research productivity in collaboration with MDs in specific subspecialties and thus help to meet the research needs of pediatric departments during the next decades.

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Differentiation of Epiglottitis From Laryngotracheitis in the Child With Stridor

Robert D. Mauro, MD; Steven R. Poole, MD; Charles H. Lockhart, MD

 To identify which clinical findings serve to differentiate acute epiglottitis from laryngotracheitis and also to evaluate the role of direct inspection of the epigiottis in the evaluation of children initially thought to have laryngotracheitis, we prospectively evaluated 155 children presenting to the emergency room with acute stridor. Three of the findings on physical examination were associated with epiglottitis: absence of spontaneous cough, drooling, and agitation. The diagnosis assigned prior to inspection of the epigiottis was incorrect in two of six patients with epiglottitis and in three of 149 patients with laryngotracheitis. The diagnosis made after inspection was correct in all 155 patients. Minor complications of Inspection were seen in seven patients with laryngotracheitis. No complications were seen in the children with epiglottitis. We conclude that drooling, agitation, and absence of cough are predictors of epiglottitis, but clinical findings alone cannot exclude epigiottitis in every child who appears to have laryngotracheitis. When laryngotracheitis is the suspected diagnosis, inspection of the epigiottis by a pediatrician in a hospital emergency room is an effective aid to the evaluation of the child with acute stridor. (AJDC 1988;142:679-682)

In evaluating the child with acute stridor, the pediatrician is frequently called on to distinguish acute epiglottitis from laryngotracheitis or viral croup. The experienced practitioner can sometimes make this distinction with confidence on the basis of a brief history and physical exami-

nation. With ambiguous presentations, however, the clinician faces a serious dilemma. Prompt recognition of acute epiglottitis is critical to ensure immediate therapy and a good outcome.¹⁻³

Certain clinical criteria are thought to be useful in distinguishing acute

For editorial comment see p 597.

epiglottitis from laryngotracheitis, 4.5 yet to our knowledge, no prospective study has identified those findings that serve to make this differentiation. Direct inspection of the epiglottis is definitive, but its role is controversial. The medical literature contains vague warnings but few data regarding the possibility that direct inspection of the epiglottis of a child with acute stridor may precipitate total airway obstruction.

We undertook this study to identify which findings in the history and physical examination serve best to distinguish acute epiglottitis from laryngotracheitis, and to evaluate the role of direct inspection of the epiglottis, performed by a pediatrician in the emergency room, in the evaluation of children initially thought to have laryngotracheitis.

PATIENTS AND METHODS

Between November 1984 and December 1985, 155 children with acute stridor presenting to the emergency room of a children's hospital were prospectively evaluated by a physician using a standardized protocol. The presence or absence of 19 findings on history and physical examination was recorded. Following the history and physical examination, an initial diagnostic impression was recorded. If the child was thought to have acute epiglottitis, a pediatric anesthesiologist was called, and direct inspection of the epiglottis was de-

ferred until his arrival. Otherwise, the epiglottis was inspected by the emergency room pediatric resident or attending physician.

Each patient underwent direct inspection of his epiglottis by each of four methods, sequentially, until an adequate view of the epiglottis was achieved. The first attempt was made with a light alone, simply asking the child to open his mouth. If that attempt was unsuccessful, a second attempt was made using a light and a wooden tongue depressor, with the child in a sitting position. If necessary, subsequent attempts were made by direct pharyngoscopy with a laryngoscope, with the child sitting, and, finally, with the laryngoscope with the child supine. A curved or straight laryngoscope blade was used, at the discretion of the examining physician. At each stage, the child was restrained by assistants as necessary.

Forceful depression of the entire length of the tongue, including the posterior third, was permitted in each attempt at inspection. Care was taken, however, not to touch the epiglottis and to avoid exposing the glottis.

The appearance of the epiglottis was recorded as normal or abnormal (inflamed) according to its color, size, and contour. The initial diagnostic impression was revised, if necessary, according to the appearance of the epiglottis. Any complications of direct inspection were recorded. Patients were managed at the discretion of the examining physician.

Charts of those patients hospitalized were reviewed after discharge. Telephone follow-up of all patients was conducted seven to 21 days after initial presentation to identify late complications and to ascertain whether the patient's subsequent course was consistent with the diagnosis assigned after direct inspection. A final diagnosis was assigned after chart review and telephone follow-up.

Each of the six children with a final diagnosis of acute epiglottitis had an inflamed, swollen epiglottis on direct inspection. All 149 patients with a final diagnosis of laryngotracheitis met each of the follow-

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From the Departments of Pediatrics (Drs Mauro, Poole, and Lockhart) and Anesthesiology (Dr Lockhart), The Children's Hospital and the University of Colorado School of Medicine, Den-

Read in part before the 33rd Annual Meeting of the Western Society for Pediatric Research, Carmel, Calif, Feb 4, 1986.

Reprints not available.

| | Final Di | gnosis* | | |
|--------------------------|----------|---------|------------|---------|
| Clinical Findings | AE | LT | χ 2 | P Value |
| Spontaneous cough Absent | 6 | 21 | 23.9 | <10-6 |
| Present | 0 | 128 | | |
| Drooling Present | 4 | 15 | 12.3 | <.001 |
| Absent | 2 | 134 | | |

^{*}AE indicates acute epiglottitis; and LT, laryngotracheitis.

| Table 2.—Spontaneous C Drooling on Physical Exan Predictors of Final Dia | nina | tion | |
|--|------|------|-------|
| | Die | Fina | |
| | ΑE | LT | Total |
| Cough absent; drooling present | 4 | 0 | 4 |
| Cough absent; drooling absent | 2 | 21 | 23 |
| Cough present; drooling present | 0 | 15 | 15 |
| Cough present; drooling absent | 0 | 113 | 113 |
| | 6 | 149 | 155 |

| *AE indicates | acute | epiglottitis; | and | LT, | laryn- |
|---------------|-------|---------------|-----|-----|--------|
| gotracheitis. | | | | | |

ing diagnostic criteria: acute stridor; negative history or diagnostic evaluation for foreign-body aspiration or ingestion; normal epiglottis on direct inspection; and no stridor or respiratory distress at telephone follow-up.

A χ^2 analysis with Yates' continuity correction was performed on 2×2 contingency tables for each of the 19 findings on history and physical examination to determine which items were associated with the final diagnosis. Because 19 separate findings were analyzed, a revised P value of $\leq .0027$ was chosen as indicating statistical significance for the analysis of each individual finding, so as to hold the experiment-wide probability of a type 1 error at .05.6

The study was conducted with the assent of The Children's Hospital (Denver) Medical Research Committee.

RESULTS Final Diagnoses

The study was completed by 155 children: 149 had laryngotracheitis as their final diagnosis, and six had acute epiglottitis. The mean age of patients with laryngotracheitis was 7.6 months (range, 2.5 months to 12.9 years). The

Table 3.—Technique Required for Adequate Inspection of Epiglottis, According to Diagnosis

| | Method by Which Adequate View Was Achieved | | Patients, No. (%) | | | |
|--|--|----|-------------------|--------|--|--|
| | | | LT* | AE* | | |
| | No instrument | 7 | (4.7) | 0 (0) | | |
| | Tongue blade | 72 | (48) | 2 (33) | | |
| | Laryngoscope, sitting | 47 | (32) | 3 (50) | | |
| | Laryngoscope, supine | 22 | (15) | 1 (17) | | |
| | Unable to view | 1 | (0.7) | 0 (0) | | |

*LT indicates laryngotracheitis; and AE, acute epiglottitis.

mean age of patients with acute epiglottitis was 3.2 years (range, 1.4 to 5.6 years). Ninety-eight patients with laryngotracheitis were admitted to the hospital, as were all six patients with acute epiglottitis. Seven additional patients with an initial diagnosis of laryngotracheitis were unavailable for follow-up.

Haemophilus influenzae type b grew from blood cultures obtained from five of the six patients with acute epiglottitis. The sixth child had two negative blood cultures as well as a negative antigen test of his urine for H influenzae type b. He had been treated with intramuscular penicillin G at another medical facility ten hours prior to his initial presentation with stridor. Group A β-hemolytic Streptococcus grew from a throat culture obtained prior to penicillin therapy.

Clinical Findings as Predictors of Final Diagnosis

The initial diagnostic impression of the examining physician was incorrect

in three of the 149 patients with laryngotracheitis. Two children were thought to have acute epiglottitis; one was thought to have an aspirated or ingested foreign body. Two of the six patients with acute epiglottitis were believed by the emergency room pediatrician to have laryngotracheitis before inspection of the epiglottis.

Nine clinical findings were assessed by history: drooling, rapid progression of illness over preceding six hours, spontaneous cough, agitation, severe sore throat, aphonia, hoarseness, somnolence, and cyanosis. None was associated with the final diagnosis. Because a history of severe sore throat, aphonia, or hoarseness might be difficult to obtain for infants, the data regarding these items were analyzed separately for children 18 months of age and older; association with the final diagnosis was again absent.

Three findings on physical examination were predictive (P < .0027) of a final diagnosis of acute epiglottitis: absence of a spontaneous cough, presence of drooling, and presence of agitation. The remaining seven items, imminence of total airway obstruction. hoarseness, muffled voice, aphonia, somnolence, retractions, and cyanosis, were not associated with the final diagnosis. The results of the χ^2 analysis are listed in Table 1. Analysis of the data for only those children 18 months old and older revealed no association between final diagnosis and either muffled voice or aphonia.

Drooling on physical examination in the absence of spontaneous cough provided the most specific indicator of acute epiglottitis (P < .001). The association of these two signs with the final diagnosis is shown in Table 2. A 2×2 contingency table was constructed to assess the ability of drooling in the absence of spontaneous cough to predict the final diagnosis. Both the specificity and the positive predictive value were 100%. Sensitivity, however, was 67%, as these two findings taken together failed to predict two of the six patients with acute epiglottitis.

Absence of spontaneous cough taken alone was the most sensitive predictor of acute epiglottitis (P<.001). All six patients with acute

epiglottitis lacked a spontaneous cough, resulting in a sensitivity and negative predictive value of 100%. The positive predictive value of this finding, however, was 22%.

Direct inspection of the Epiglottis

The final diagnosis agreed with the diagnosis assigned immediately after direct inspection of the epiglottis in all 155 patients. Table 3 lists the technique by which each child's epiglottis was inspected. We were unable to adequately view the epiglottis of one child with laryngotracheitis, a 4½-year-old boy, who fought the examination too vigorously to permit an adequate inspection without unacceptable risk of trauma to his mouth and teeth.

The mean elapsed time between direct inspection of the epiglottis and tracheal intubation was 62 minutes (range, 25 to 140 minutes) in the six children with acute epiglottitis. In two patients, inspection of the epiglottis was initially performed by the private pediatrician in his office before referral to our hospital for confirmation and management.

Of the six patients with acute epiglottitis, none experienced complications attributed to direct inspection of the epiglottis. One patient with acute epiglottitis developed acute airway obstruction associated with cyanosis and bradycardia 25 minutes after direct inspection, as he was being taken into the operating room for intubation. This complication was attributed to the natural progression of acute epiglottitis, given the time elapsed between direct inspection and the occurrence of airway obstruction.

Of the 149 patients with laryngotracheitis, seven experienced minor complications attributable to direct inspection of the epiglottis. Three children vomited, without evidence of aspiration of their vomitus. Two children became cyanotic briefly during the inspection. One child experienced a small crack in her lip, which bled for one to two minutes. In one child, a 5½-year-old girl, direct inspection resulted in a small chip in one of her primary central incisors.

COMMENT

Our attempt to identify specific clinical findings for differentiating between acute epiglottitis and laryngotracheitis indicates that direct observations made by the physician are more reliable than the parent's recounting of those same variables. The observed presence or absence of cough and drooling was predictive of the final diagnosis, but not perfectly so. As Table 2 shows, these variables alone would have permitted a correct differentiation of acute epiglottitis from larvngotracheitis in 132 of 155 patients. In the remaining 23 patients with neither a spontaneous cough nor drooling, however, the diagnosis could not be predicted from these variables alone.

We identify two limitations to the interpretation of these data. First, given the small number of patients with acute epiglottitis in our study. the occurrence of these clinical findings is poorly estimated. If the true prevalence of spontaneous cough in children with epiglottitis is, in fact, greater than 0%, the ability of that finding to predict the final diagnosis would diminish. Second, the prevalence of epiglottitis in our study was 4% (6/155). If the sensitivities and specificities obtained herein are applied to a population with a lower prevalence of epiglottitis, the predictive values of these findings will decrease.

The definitive diagnosis of acute epiglottitis requires direct inspection of the epiglottis. At the University of Colorado Affiliated Hospitals, Denver, our practice for many years has been to inspect the epiglottis of any child with acute stridor in whom the diagnosis of epiglottitis is considered. If the pediatrician suspects epiglottitis as the likely diagnosis, inspection is delayed until an anesthesiologist or pulmonologist arrives. If, on the other hand, the pediatrician believes that acute epiglottitis is unlikely yet still harbors some residual doubt, then the pediatrician inspects the epiglottis independently in the emergency room.

Our results demonstrate the efficacy and ease of this practice. A concern at the outset of our study was whether pediatricians viewing the ep-

iglottis of a child with stridor could reliably identify the appearance as normal or inflamed. In each of the 149 patients with suspected laryngotracheitis in whom a pediatrician inspected the epiglottis without assistance, the pediatrician was able to interpret the epiglottis as unequivocally normal or abnormal. Rapkin' has suggested that the "epiglottis may not be seen easily" in many children with acute stridor. He reported that gentle examination of the pharynx failed to provide an adequate view of the epiglottis in 33 of 47 children with laryngotracheitis and in all three children with acute epiglottitis. In our study, we found that use of a tongue blade alone was sufficient to provide an adequate view in more than half of the patients with laryngotracheitis. Use of the laryngoscope provided an adequate view in virtually every other patient, regardless of diagnosis.

Is direct inspection of the epiglottis safe in a child with acute stridor who may have epiglottitis? The medical literature, unfortunately, provides no objective basis for estimating that risk. Caveats abound, with few data apparent in support of various authors' opinions. A review of the literature identified only two reports, both retrospective chart reviews, in which children with acute epiglottitis were said to have experienced complete airway obstruction as a result of inspection of the epiglottis. 8,8 Neither report notes the number of children in whom this complication was said to have occurred or the elapsed time from inspection to total airway obstruction. Without this information, it is impossible to infer whether inspection of the epiglottis was the likely cause of complete obstruction. The natural course of acute epiglottitis is rapidly progressive; sudden, total airway obstruction is well recognized in these children, even in the absence of pharyngeal manipulation.8-12

In contrast, Diaz and Lockhart¹³ found no complications of direct inspection in 104 children with acute epiglottitis. Greenberg and Schisgall¹⁴ inspected the epiglottis of 21 children with acute epiglottitis without untoward effect. Both of these retrospective studies suffer the same limitations

noted above.

Given the current paucity of data, we cannot exclude the possibility that inspection of the epiglottis of a child with acute epiglottitis may entail a risk of precipitating airway obstruction. When epiglottitis is thought to be likely, on clinical grounds, we recommend awaiting the arrival of a physician skilled in establishing a reliable airway before inspection of the epiglottis is attempted.

Our study focused on a narrower question: whether direct inspection of the epiglottis by the pediatrician in the emergency room has a role in the definitive evaluation of the child who is initially thought to have laryngotracheitis. With a total of only six children with acute epiglottitis in our study, we can draw no conclusion regarding the safety of this practice for those children initially thought to have laryngotracheitis who prove to have acute epiglottitis. It is critical to recognize, however, that the risk of direct inspection in these patients must be weighed against the risk of delaying or missing the diagnosis of acute epiglottitis in a child who presents with acute stridor. Even if admitted to the hospital for observation and treatment of prechildren sumed laryngotracheitis,

with unsuspected epiglottitis may experience sudden, life-threatening deterioration. 10 Our sample is instructive in that the diagnosis of epiglottitis would have been missed, on clinical judgment alone, in two of the six patients with acute epiglottitis.

The lateral neck roentgenogram has been used in previous studies7,15 to assist in the differentiation of acute epiglottitis from laryngotracheitis. Although Rapkin⁷ found interpretation of the lateral neck roentgenogram by pediatricians to be successful, the interpretation by pediatric residents and attending physicians, in our experience, is too often equivocal. Diaz and Lockhart13 found that 14 of 20 lateral neck roentgenograms taken in children with proved acute epiglottitis showed a normal epiglottis, with hypopharyngeal dilatation as the only roentgenographic indicator of disease. Jones and Holland¹⁶ found that about 30% of normal lateral neck roentgenograms were read as falsely positive by attending emergency room physicians and radiologists. Moreover, numerous authors1,10,17,18 have cautioned that the delay inherent in this procedure may result in spontaneous airway obstruction in a department of the hospital where prompt resuscitation is difficult. We speculate, on the basis of our prospective study, that direct inspection of the epiglottis may be more definitive than lateral neck roentgenograms. Direct inspection is certainly quicker and less expensive. Determination of whether it is safer awaits further study.

Stridor is a common pediatric symptom, and the determination that the child does not have acute epiglottitis cannot be made by consulting an airway specialist in every case. Following our approach, we were able to make a quick and correct diagnosis of acute epiglottitis or laryngotracheitis in all 155 children presenting with acute stridor. A pediatric anesthesiologist was called to assist in the inspection of the epiglottis in six patients, resulting in the diagnosis of four cases of epiglottitis. In the remaining 149 patients, the epiglottis was viewed by a pediatrician, identifying the two remaining patients with acute epiglottitis and placing only those two children "at risk" for developing complications of direct inspection without an airway specialist present.

James K. Todd, MD, Dennis Luckey, MS, PhD, Leland Fan, MD, and Barton D. Schmitt, MD, gave critical reviews of the manuscript; Suzanne Glaser, RN, assisted with telephone follow-up; and Beth Becker assisted with data entry.

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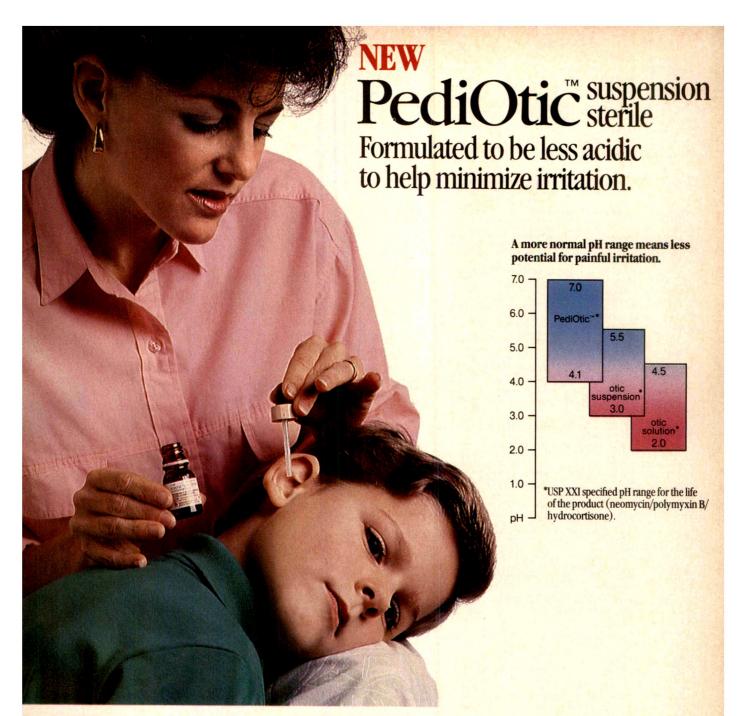
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Special Features

Radiological Case of the Month

James H. McClenathan, MD (Contributor); Beverly P. Wood, MD (Section Editor)

A 10-year-old girl was admitted for evaluation of an 8.1-kg weight loss. Two weeks before admission, she had an episode of "stomach flu" with fever, epigastric pain, nausea, and vomiting. These symptoms improved temporarily, but several days later abdominal pain and vomiting recurred, with no loss of appetite. Daily abdominal pain was relieved by vomiting. The emesis was bilious and contained undigested food.

At physical examination, she weighed 27.9 kg and appeared emaciated; a soft murmur was heard on the left side of her neck. She was slightly exophthalmic. Thyroid function tests and an upper gastrointestinal tract series were performed (Figure).

Accepted for publication May 12, 1987. Contributed from the Department of Surgery, Kaiser Permanente Medical Center, Santa Clara, Calif.

Reprint requests to the Department of Radiology, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642 (Dr Wood).

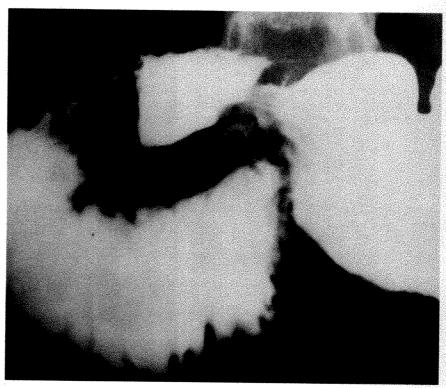


Figure.

Denouement and Discussion

Hyperthyroidism as a Cause of Superior Mesenteric Artery Syndrome

Upper gastrointestinal tract series shows dilatated duodenum with lack of barium passage beyond third portion of duodenum.

The upper gastrointestinal tract series showed normal stomach, pylorus, and duodenal bulb. The second and third portions of the duodenal sweep were dilated, with a sharp cutoff of barium flow at the junction of the third and fourth portions of the duodenum. There was delay in passage of barium past this point. This is the level at which the superior mesenteric artery crosses the duodenum. A trial of conincluding servative management, small liquid feedings and positioning the patient in prone and decubitus positions, was unsuccessful. She continued to vomit and lost another 0.9 kg. Thyroid test results indicated markedly elevated thyroid function. The serum thyroxine level was 411 nmol/L (31.9 µg/dL) (normal range, 58 to 148 nmol/L [4.5 to 11.5 μ g/dL]).

Therapy with propylthiouracil and an oral solution of potassium iodide (SSKI, Upsher-Smith Laboratories Inc, Minneapolis) was begun. Because management of her weight loss and vomiting had failed, hyperalimentation via a central line was started. She gained 7.65 kg during the next 17 days. When the patient's weight had returned to 34.65 kg, she tolerated an unrestricted diet without any vomiting or pain and was discharged three days later. Her thyroid function returned to normal during the first month of treatment, and she was well at a follow-up evaluation 18 months later.

Von Rokitansky¹ first suggested that the duodenum could be obstructed where it passes beneath the superior mesenteric vessels and over the spine. A number of reports have documented that children can be affected by this condition.²⁻⁵ The most common symptoms of such obstruc-

tions are vomiting, nausea, and epigastric pain. Upper gastrointestinal radiography demonstrates marked dilatation of the second portion of the duodenum down to the right of the spine. There is rapid churning peristalsis within the proximal duodenum and apparent obstruction at the site where the duodenum crosses the spine. Most patients also have significant weight loss or lack appropriate weight gain. Diagnosis is established by an upper gastrointestinal tract series. Thyrotoxicosis and its concomitant rapid weight loss may produce this syndrome of duodenal obstruction. The mechanism of obstruction is related to the vulnerable location of the third portion of the duodenum as it crosses the spine at the level of L-3. Just to the right of the spine, the duodenum passes beneath the retroperitoneal attachments of the mesentery, and at this level extrinsic obstruction may occur in asthenic persons. The superior mesenteric artery (SMA) itself branches from the aorta at the level of L-1, which is cephalad to the site of obstruction and is usually not likely to be the cause of compression. Weight loss or placing of patients in a body cast may create drag upon the small bowel and cecum, tightening the pressure created by the mesenteric attachments.

Burrington and Wayne⁴ have shown that patients in whom SMA syndrome develops fit into four disease categories: (1) congenital, (2) rapid weight loss, (3) rapid growth without weight gain, and (4) hyperextension of the spine in a cast or brace. This patient fits the second category.

Patients with mesenteric compression of the duodenum should initially be managed conservatively by small

liquid feedings and positioning on the right side or prone. If a cause of rapid weight loss is identified, it should be corrected. Parenteral nutrition may be required.

Surgical management of patients with SMA syndrome is controversial. Gastroenterostomy, duodenojejunostomy, and mobilization and repositioning of the duodenum are three methods of managing patients with SMA syndrome. Operative treatment is rarely necessary.^{2-4,6,7}

This patient demonstrated the classic findings of SMA syndrome produced by hyperthyroidism with weight loss. Her symptoms were relieved by alleviating the hyperthyroidism and initiating a course of parenteral hyperalimentation. The SMA syndrome is an unusual cause of gastrointestinal tract obstruction in children, but this cause should be considered when the more common causes are unlikely.

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Radiological Case of the Month

Jai Kishan, MD; Nissar A. Mir, MB;
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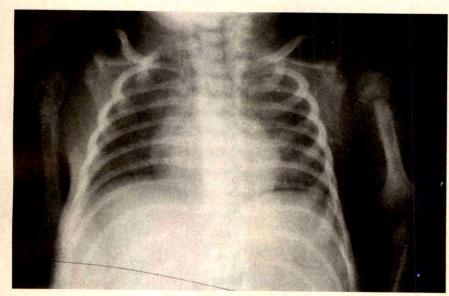


Figure 1.



Figure 2.



Figure 3.

A 6-week-old male infant was admitted to the nursery with a threeday history of fever, lethargy, and regurgitation of feedings. The infant had been full-term at birth. A detailed history of the family and social circumstances yielded no information to suggest child abuse or accidental trauma.

On physical examination, the infant was febrile (temperature, 40°C) and had generalized muscular hypertonicity and a bulging anterior fontanelle. Cerebrospinal fluid (CSF) examination showed a white blood cell count of 1.5×10^{9} /L (1500/mm³), a glucose level of 1.7 mmol/L (30 mg/dL), and a protein level of 2.15 g/L (215 mg/dL). The CSF culture yielded Klebsiella pneumoniae. The infant was administered parenteral gentamicin and chloromycetin. Ten days later, he had a tender swelling of the left shoulder. His white blood cell count was 37.2×109/L $(37.2 \times 10^3 \text{/mm}^3)$ with 0.50 (50%) band cells and an erythrocyte sedimentation rate of 17 mm/h (first hour). Roentgenograms of both upper limbs (Fig 1) were obtained. One week later, the infant had swelling of both the knees and the upper part of the left forearm. Roentgenograms of both lower limbs (Fig 2) and the left upper limb (Fig 3) were obtained. The results of other laboratory tests were as follows: IgG, 51.2 g/L (512 mg/dL); IgM, 7.4 g/L (74 mg/dL); IgA, 2.4 g/L (24 mg/dL); complement C3, 10 g/L (100 mg/dL); C4, 2.7 g/L (27 mg/dL); and a negative VDRL test result. Left tibial aspirate material yielded K pneumoniae.

Accepted for publication by Lionel W. Young, MD, former section editor, March 4, 1987.

Contributed from the Department of Pediatrics, Faculty of Medicine, Al Arab Medical University, Benghazi, Libya.

Reprint requests to Children's Hospital Medical Center of Akron, 281 Locust St, Akron, OH 44308 (Dr L. W. Young).

Denouement and Discussion

Klebsiella Multifocal Osteomyelitis

Fig 1.—Roentgenogram showing soft-tissue swelling and radiolucent areas in upper ends of both humeri and pathologic fracture of left humerus.

Fig 2.—Roentgenogram of both knees showing bilateral osteolytic lesions, periosteal reaction, and pathologic fractures of distal ends of femurs and proximal ends of tibias.

Fig 3.—Roentgenogram of left upper limb showing pathologic fracture of proximal humerus with periosteal reaction and multiple osteolytic lesions and periosteal reaction of radius.

The clinical manifestations of osteomyelitis in children vary with age. Neonatal osteomyelitis has long been considered different from osteomyelitis in older children.1 In neonates, most bone infections are hematogenous and most often involve the metaphyses. The agents that cause osteomyelitis in the newborn are the organisms that cause neonatal septicemia. The relative incidences of such agents have changed over the past four decades. Between 1940 and the mid-1960s, almost 85% of the osseous infections in neonates were caused by Staphylococcus aureus.2 In the early 1970s, Streptococcus agalactic (group B streptococci) emerged as an important neonatal pathogen, and today more than 50% of bone infections in the newborn are caused by this organisms; Saureus and enteric bacilli are less frequent bacterial causes.4 Osteomyelitis usually occurs in neonates during the first two weeks of life. The most common sign of neonatal osteomyelitis is limitation of spontaneous movement.5 Other physical signs are localized tenderness, ery-

thema, and swelling.

Associated septic arthritis occurs in 75% of neonatal osteomyelitis cases.8 Multiple sites of involvement are frequent.6 Early in the course of the disease, roentgenography and radionuclide scintigraphy of bone may yield normal results.7 Metaphyseal bone destruction and periosteal reaction are roentgenographic findings that develop later.1 Pathologic fracture in infantile osteomyelitis, as in this patient, is uncommon. Pathologic fracture in S aureus osteomyelitis of the femur has been reported in a 4-week-old infant.8 Aspirates of subperiosteal pus or metaphyseal fluid yield a pathogen in 70% of cases.1 However, organisms also may be recovered from blood (cultures have yielded organisms in 60% of children)1 and CSF. Indirect evidence of bacterial antigens by latex agglutination or countercurrent immunoelectrophoresis may be useful in the absence of yield of organisms by cultures.

Antimicrobial therapy is usually initiated with a combination of penicillinase-resistant penicillin and an

aminoglycoside.² The recommended duration of antibiotic therapy is four to six weeks. The occurrence of chronic osteomyelitis is rare.²

This infant had *K* pneumoniae meningitis and subsequent *K* pneumoniae osteomyelitis at multiple sites. Normal remodeling of the involved bones and no residual deformity were noted on follow-up examination at age 14 months.

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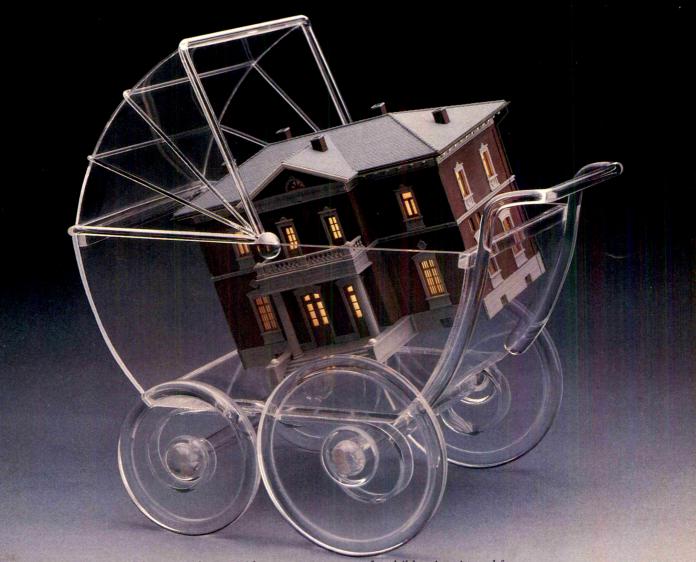
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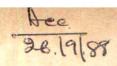
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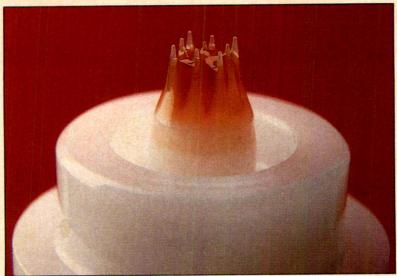
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2. Donaldson JC, Elliott RC: A study of co-positivity of three multi-puncture techniques with intradermal PPD tuberculin. AM Rev Resp Dis 118:843-846, 1978.



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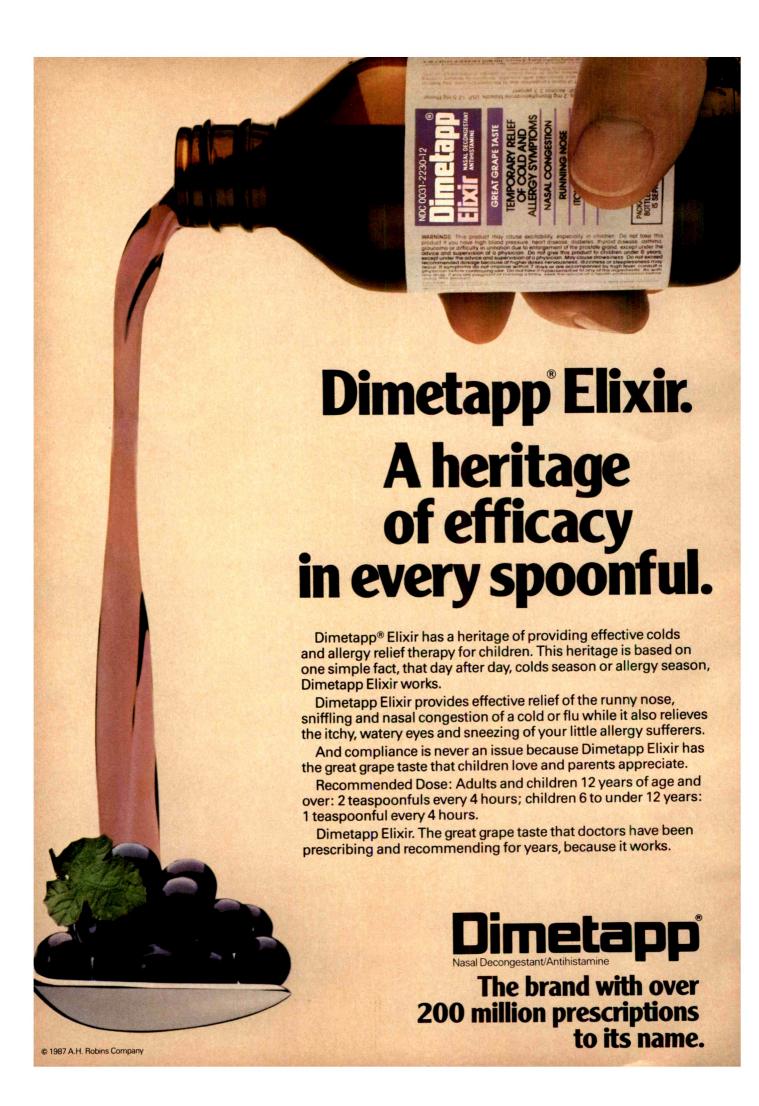
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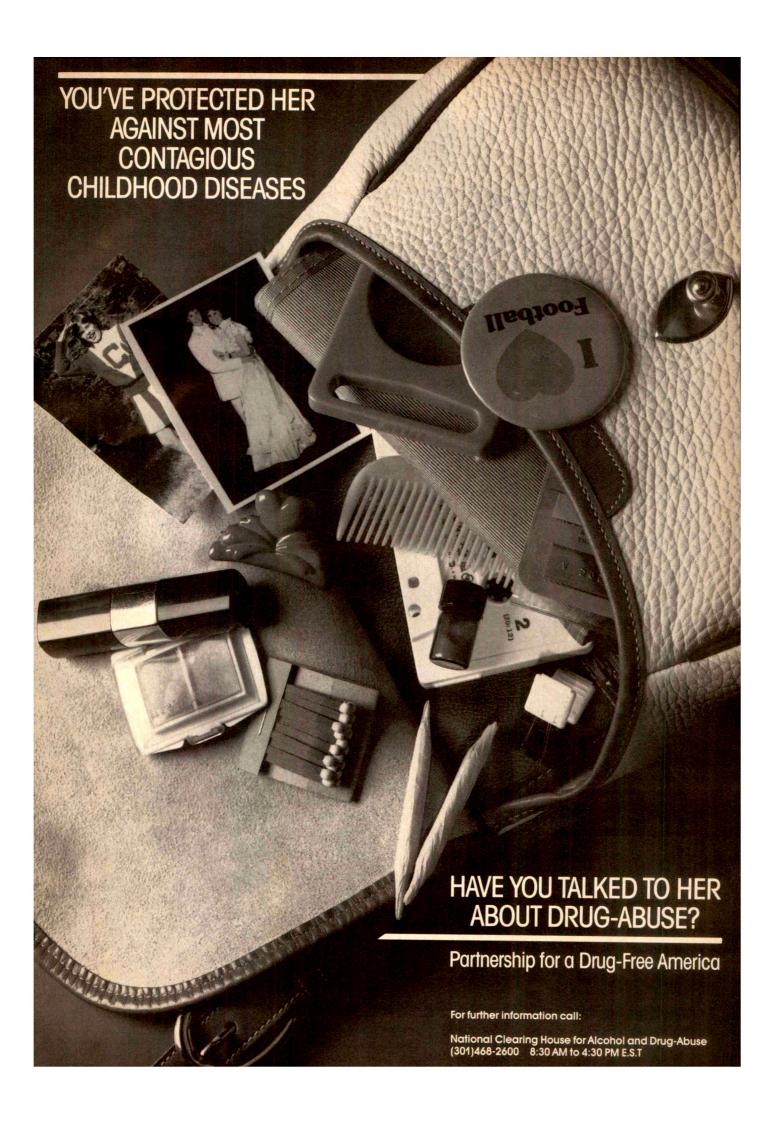
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Ribavirin and Respiratory Syncytial Virus-Associated Apnea

Sir.—In his editorial on the use of ribavirin to treat respiratory syncytial virus (RSV) infections, published in the May 1988 issue of the AJDC, Ray¹ poses a number of unresolved questions and invites readers to add to his list. While there is a well-known association between RSV infections and apnea, especially in young infants or those with a history of prematurity,² it is not known if treatment with ribavirin is either warranted or effective in infants in whom apnea is the major, and sometimes the only, manifestation of infection.

Patient Reports.—Patient 1.—A 25day-old full-term male infant who was normal at birth, except for a hemodynamically insignificant ventricular septal defect, was admitted after having had a prolonged apneic episode accompanied by profound cyanosis while at home. The infant had had two to three days of mild nasal congestion before this episode. The infant responded to bag-and-mask ventilation but experienced a respiratory arrest within two hours of arrival at the hospital. The infant was successfully resuscitated and sustained by mechanical ventilation for 20 hours. The results of the workup, which included cultures of the blood and cerebrospinal fluid, were normal, except for the finding of a left upper lobe infiltrate on chest roentgenogram. The RSV was identified by rapid viral diagnosis on material obtained via nasopharyngeal aspiration. The infant was treated with aerosolized ribavirin for three days and was discharged home in good condition after seven days.

PATIENT 2.-A 22-day-old full-term infant was admitted with the diagnosis of bronchiolitis. The RSV was identified by rapid viral diagnosis on material obtained via nasopharyngeal aspiration and was subsequently confirmed by viral culture. During continuous cardiorespiratory monitoring, initiated because of the patient's age, the infant was noted to have several episodes of apnea, some accompanied by mild bradycardia (pulse rate per minute in the 80s), that resolved with stimulation. Frequent episodes of apnea were confirmed by a pneumogram. Ribavirin therapy was initiated, though the infant had only mild to moderate symptoms of respiratory distress, because of the apnea and the young age. At the conclusion of three days of therapy, the ribavirin was discontinued,

but the infant continued to have episodes of apnea with mild bradycardia. A second rapid viral diagnosis indicated RSV (though the viral culture was subsequently negative), and the infant was treated with another three-day course of ribavirin therapy. Another pneumogram after conclusion of this second course of ribavirin was also abnormal, and the patient was discharged with home apnea monitoring. The infant experienced many episodes of apnea, all responsive to stimulation, while being monitored at home and was successfully weaned from the home monitor at 6 to 7 months of age.

Comment.—The use of ribavirin to treat RSV infections is currently under critial review. 1,3 The Committee on Infectious Diseases of the American Academy of Pediatrics published guidelines for the use of ribavirin over one year ago and included as candidates for treatment "infants . . . hospitalized with lower respiratory tract disease that is not initially severe, but who may be at some increased risk of progressing to a more complicated course by virtue of young age (<6 weeks)."4 Hall et al5 demonstrated that the presentation of RSV infections in neonates is often atypical with "significantly less lower-respiratory-tract involvement" and that the disease "may be overlooked" in these patients. Two (9%) of the patients in that study died suddenly and unexpectedly.

The two patients described herein raise many questions regarding the proper management of very young infants with suspected or confirmed RSV infection. The second infant presented in the winter of 1987, close to the time when the American Academy of Pediatrics guidelines were published. It is uncertain if many would treat that infant with ribavirin today. The first patient is more worrisome and raises many questions regarding RSV infections and the use of ribavirin in the treatment of very young infants with respiratory tract infections. Is ribavirin effective therapy for the apnea associated with RSV? Should very young infants with only upper respiratory tract symptoms be tested for RSV infection? Should they be hospitalized and monitored for apnea? Should they be treated with ribavirin?

RANDY ROCKNEY, MD

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Fetal Neglect as Child Abuse

Sir.—I read with interest the article by Fleisher regarding wrongful births. While I certainly agree with looking into actions taken intentionally, such as drug use, I believe we should also be looking at actions that are intentionally not taken. As an example I present the case of a pregnant, 19-year-old mother who had an 8-month-old first child (the product of a 37-week gestation with preterm labor) and who was given tocolytics and intensive educational programs for the last five weeks of her first pregnancy. The mother chose not to receive prenatal care until approximately 22 weeks' gestation, even though she knew she was pregnant. At 23 weeks' gestation of her current pregnancy. she began having contractions at 8 AM. She recognized the contractions for what they were, but did not seek advice from anyone until approximately 2 PM, when she was told to come to the hospital immediately. The mother did not arrive there until approximately 7 PM, at which time her cervix was dilated 8 cm. Two hours later she was delivered of a 23-weekold fetus that died within 24 hours. While there was no child who could

sue for injuries, this mother's lack of action certainly seemed to have had a very strong impact on the death of this fetus.

As a member of our local and state child protection team for several years, I wonder where this falls in the broad spectrum of child abuse. I also have no answers, but only some very painful questions. Thank you for tackling this difficult issue.

BARBARA P. YAWN, MD Worthington Medical Center 508 Tenth St PO Box 86 Worthington, MN 56187-0086

1. Fleisher LD: Wrongful births: When is there liability for prenatal injury? AJDC 1987;141: 1260-1265.

In Reply.—Dr Yawn's letter presents a case in which a young woman, who apparently had knowledge of and access to medical services, did not seek prenatal care until it was too late to save her 23-week-old fetus. It is an example of a sad and frustrating experience that must sometimes be faced by obstetricians and family practitioners, particularly those in areas with residents of low socioeconomic status where routine medical visits are not the norm. However, as I pointed out in my article on wrongful births,1 the question of whether a pregnant woman has a legally enforceable duty to act nonnegligently to protect the health of a fetus she apparently intends to carry to term is not an easy one to answer. Moreover, especially given the unrelenting hostility of the current administration to women's reproductive rights (eg, the new regulations promulgated by the US Department of Health and Human Services to implement Title X of the Public Health Services Act, 42 USC §300a-6 [1982] [family planning services], which forbid nondirective options counseling for pregnant women), it appears to be a problem for which any suggested solution is likely to do more harm than good.

To begin with, instances of potential fetal neglect cannot easily be categorized within "the broad spectrum of child abuse." Although prematernal behavior can and does dramatically affect the life and health of a child after birth, the uncertain legal status of even a viable fetus and its position within the body of a competent adult are not factors to be disregarded

lightly. From a legal standpoint, any action taken to coerce a woman who is 22 or 23 weeks pregnant into acceding to medical advice—or to force her to refrain from certain deleterious behavior—is unlawful under Roe v Wade (410 US 113 [1973]) as an infringement on a woman's constitutionally protected right to autonomy and bodily integrity during her pregnancy. As the American College of Obstetricians and Gynecologists recently concluded, "[t]he use of judicial authority to implement treatment regimens in order to protect the fetus violates the pregnant woman's autonomy."2

Putting Roe v Wade and its important teachings aside, the case presented by Dr Yawn does not lend itself to any practical solution. I do not believe that we as a society are prepared to institutionalize women, even those suspected of fetal neglect, for up to four or five months of their pregnancy, or to get involved in at-home surveillance efforts. Even were we willing to do so, how early would such surveillance begin? We already know, for example, that heavy alcohol drinking during the first trimester of pregnancy may have the greatest effect on the development of the fetus. Yet are we willing to monitor all women monthly to assure (1) that they are not pregnant or (2) that they are behaving nonnegligently if they are pregnant?

Perhaps the best way to assure that pregnant women avoid seeking prenatal care altogether is to threaten them with coercion or restraint should their behavior fall below some preordained minimum. We stand the greatest chance of improving prenatal care, and thus fetal health, by encouraging trusting physician-patient relationships. Physicians can counsel pregnant women and thereby inform prematernal behavior; they can encourage and provide access to appropriate prenatal care. They cannot, however, do more. "Actions of coercion to obtain consent or force a course of action limit maternal freedom of choice, threaten the doctor-patient relationship, and violate the principles underlying the informed consent process."2

Lynn D. Fleisher, PhD, JD Sidley and Austin One First National Plaza Chicago, IL 60603

- 1. Fleisher LD: Wrongful births: When is there liability for prenatal injury? *AJDC* 1987;141: 1260-1265.
- 2. American College of Obstetricians and Gynecologists: Committee Opinion No. 55. October 1987

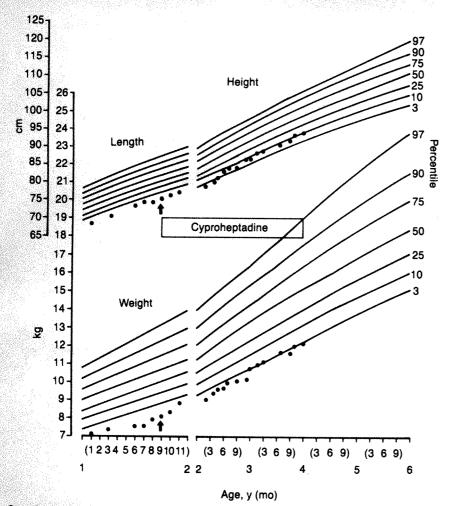
Cyproheptadine and Growth

Siz-It is well known that cyproheptadine hydrochloride (an antihistamine with serotonin-antagonistic activity) has an appetite-stimulating effect and promotes weight gain.1,2 However, its effect in promoting linear growth in association with weight gain often seems to be overlooked although it has been documented.3-5 We therefore wish to report our observations during 29 months of cyproheptadine administration in a small-for-gestational-age female infant to reemphasize the usefulness of this low-cost drug therapy for growth enhancement.

Patient Report.—A 4-year-old girl had been born normally to a 28-year-old woman after a 40-week gestational period. The infant's birth weight had been 2.32 kg (<third percentile); length, 45 cm (<third percentile); and head circumference, 29 cm (<third percentile). The cause of intrauterine growth retardation was unknown. There were no anomalies, and psychomotor development was entirely normal. The patient had no remarkable feeding problems, but her appetite was low

At the age of 1 year 8 months, she was referred to our department because of delayed physical growth. On physical examination, she appeared to be in good health, but her stature was proportionally small. Her weight was 7.91 kg (<third percentile) and length was 74.8 cm (<third percentile) (midparental height, 161.5 cm). Results of neurologic and physical examinations were normal. Bone age was 1 year 6 months (Greulich and Pyle's atlas). Until the time of examination, she had been growing at almost-normal velocities for body weight and length but exhibited no catch-up growth (Fig-

Her delayed growth was considered to be due to intrauterine causes. To increase her appetite and food intake, cyproheptadine hydrochloride administration (2 mg/d in two divided doses) was started at 1 year 9 months of age. The patient's growth during the subsequent 29-month period is shown in the Figure. The dose of cyproheptadine was not changed. Increase in weight was observed soon after cyproheptadine administration, but increase in linear growth only became apparent six months after the start of administration. No drowsiness was observed.



Growth chart for girls, including growth curve in our patient. Arrows indicate start of cyproheptadine hydrochloride administration.

Comment.—The effect of cyproheptadine therapy on both weight gain and linear growth was first demonstrated by Lavenstein et al.3 The mechanisms through which these effects of the drug are mediated are yet to be elucidated. A sustained increase in energy intake should enhance the growth-stimulating action of growth hormone,5,6 although it has been demonstrated that growth hormone secretion stimulated by deep sleep may be affected by a serotonin antagonist and acute growth hormone response to growth hormone releasing hormone after feeding is blunted. 7.8 Recently, approaches other than the use of biosynthetic human growth hormone for the treatment of certain forms of constitutional short stature have been discussed.8,9 However, particularly in certain small children, such as those born as small-for-gestational-age infants who show poor weight gain and no catch-up growth, we consider that

use of cyproheptadine therapy for promoting both weight and height gain may well be advantageous and certainly worth trying.

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Esophageal Foreign Body Presenting With Altered Consciousness

Sin—We noted the occurrence of altered consciousness as a presenting symptom in three patients with lodged foreign bodies. When a patient with altered consciousness presents, a lodged esophageal foreign body should be considered.

Patient Reports.—Patient 1.—An 8-month-old male infant presented with a choking episode that was immediately followed by 15 minutes of unresponsiveness. Paramedics found the infant unresponsive and limp. Pulse rate was 126 beats per minute, and respirations were 44/min. During transport, the patient choked, coughed up a large amount of sputum, and became more responsive.

On physical examination, the infant preferred to sleep but was easily aroused. Pulse rate was 160 beats per minute, respirations were 20/min, blood pressure was 90/54 mm Hg, and rectal temperature was 37.3°C. The remainder of examination yielded normal results.

A lateral neck roentgenogram revealed a coin-shaped foreign body in the cervical esophagus. A penny was removed by rigid endoscopy with the patient under general anesthesia.

Patient 2.—A 14-month-old male infant presented with sudden onset of gagging that occurred while he was seated at a fast-food restaurant. The patient reportedly had had a handful of pennies. Following the initial gagging episode, there were two episodes of stiffening and the eyes rolling back.

Physical examination revealed an alert and active child. Pupils were equal and reactive to light. Lungs were clear to auscultation. The heart rhythm was regular with no murmurs. Muscle strength and reflexes were normal.

Immediately following the physical examination, he became limp and unresponsive. Pulse rate was 160 beats per minute, respirations were 28/min, and blood pres-



Lateral neck roentgenogram of patient 2. Note three pennies visible in cervical esophagus.

sure was 120/80 mm Hg. Intramuscular naloxone hydrochloride (100 µg) was administered, with no change in level of consciousness. During the next hour, the patient became progressively responsive. Chest and lateral neck roentgenograms revealed three coins in the cervical esophagus (Figure). Three pennies were removed under direct endoscopy with the patient under general anesthesia. Preoperative medications included atropine sulfate.

PATIENT 3.—A 9-month-old male infant was noted to be chewing on something while seated on a couch at home. He had just completed his routine two-hour nap. After his mother searched his mouth, he gagged and vomited a piece of paper. He then became listless and fell asleep. After vigorous stimulation, the child awoke and refused breast-feeding. He had several similar brief "napping" episodes on the way to the hospital, which was a change from his usual activity. Physical examination revealed a well-developed child without stridor or retractions. Pulse rate was 120 beats per minute. During roentgenographic examination, the child gagged and again was difficult to arouse. He then became alert with stimulation. A single coin was pushed into the stomach by an esophageal dilator without incident.

Comment.—To our knowledge, altered consciousness as a presenting sign for esophageal foreign body has not been previously reported. The typical symptoms for esophageal foreign body are choking, coughing, difficulty in swallowing, pain, dysphagia, or respiratory distress. ¹⁻³ Removal is essential to prevent life-threatening complications, such as aspiration or perforation.

The pathophysiologic features of altered consciousness secondary to a

lodged esophageal foreign body are unknown. Possible explanations include transient hypoxia, exaggerated vagal response, or vasovagal syncope related to the pain of the acute ingestion. An esophageal foreign body compressing the trachea can cause hypoxia. Excess stimulation of the posterior aspects of the pharynx or esophagus may produce an exaggerated vagal response and subsequent bradycardia, hypotension, and decreased cerebral perfusion.

The transient or fluctuating nature of altered consciousness that occurred in our patients may be explained by considering a combination of the three mechanisms described above. Patients 1 and 3 most likely had a brief exaggerated vagal response (syncopal episode). Foreign bodies commonly lodge at the junction of the striated cricopharyngeal muscle and the smooth muscle of the lower portion of the esophagus because of the strong contractions of the striated muscles. The vagal response from stimulation of the cricopharyngeal muscle may greater than that produced from stimulation of smooth muscles. Thus, an exaggerated vagal response would occur with passage of the foreign body to the proximal third of the esophagus.

In patient 2, the possibility of a brief hypoxic episode secondary to temporary direct obstruction of the trachea must be considered since three coins were ingested.

Why all patients who ingest a foreign body or have a lodged esophageal foreign body do not experience an altered state of consciousness is unknown. Variability of vagal response from one patient to the next and degrees of posterior pharynx stimulation are possible explanations. Variability of vagal response is illustrated in a previously reported case of a child with swallowing syncope. She experienced complete loss of consciousness and bradycardia while eating.

The amount of posterior pharynx and esophageal stimulation may also vary depending on the size and number of foreign objects and on the amount of associated coughing and gagging. Excess stimulation of the posterior pharynx with suctioning during the initial stabilization of a newborn is known to cause bradycardia and apnea.⁵

Finally, the myocardium may be more sensitive to vagal reflexes in the presence of hypoxia and/or hypercar-

Treatment of these patients should include esophagoscopy rather than blind procedures as well as preoperative atropine administration. We recommend including esophageal foreign body in the differential diagnosis of sudden onset of altered consciousness.

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A Hazard of Using Adult-Sized Weighted-Tip Enteral Feeding Catheters in Infants

Sin—Diarrhea and hypernatremic dehydration are common in infants being fed nasoenterally. 14 We recently observed these complications in an infant transferred to our center after intraluminal migration of an adult-length weighted-tip enteral feeding tube. Occasionally, adult-length tubes are used in infants for routine nasogastric feeding. Our report is intended to alert pediatricians to the potential hazards of this practice and to suggest that the risk of complications can be reduced by using standard infant-sized nasogastric tubes.

Patient Report.—A 2.1-kg female infant was delivered at 32 weeks' gestation after an uncomplicated pregnancy. A large immature teratoma involving the right temporal lobe was found during an examination because of apnea when the infant was 5 weeks old. Nasoenteral feeding with an 8-F×102-cm radiopaque silicone elastomer feeding catheter with a silicone-weighted tip was begun after preoperative chemotherapy and craniotomy because of apnea and choking due to nasopharyngeal extension by the tumor. Satisfactory tube position in the duodenum was confirmed by serial roentgenograms. A hyperosmolar in-

fant feeding formula was infused continuously over the next 14 days to a maximum rate of 16 mL/h, after which the nasoenteral tube was expelled from the gut by vomiting associated with chemotherapy. An abdominal roentgenogram taken after the tube was reinserted disclosed the presence of a length of coiled tubing in the stomach. Nasogastric feeding was resumed without further adjustment of the tube's position, and the infant was transferred to our center.

Initial assessment was of a thin, active 2.5-kg infant with multiple neurological and ophthalmologic abnormalities associated with progressive intracranial teratoma. Laboratory tests at admission disclosed a mild metabolic acidosis (sodium, 139 mmol/L; potassium, 3.9 mmol/L; chloride, 109 mmol/L; bicarbonate, 14 mmol/L; creatinine, 10 μ mol/L; and calcium, 2.12 mmol/L). The rate of tube feeding was increased to 20 mL/h (192 mg/kg/24 h). During the subsequent 48 hours, she more frequently passed stools described as "acholic" and "the color of feeds," but her general condition, weight, and serum chemistry values remained stable. The infusion rate was decreased to 18 mL/h. The next day, her general condition deteriorated rapidly, she lost 16% (400 g) of her body weight, and the volume and frequency of the palecolored stools increased. Repeated serum chemistry evaluations showed a sodium level of 169 mmol/L, a potassium level of 4.0 mmol/L, a chloride value of 141 mmol/L, a bicarbonate value of 10.4 mmol/ L and a creatinine value of 40 µmol/L. Resuscitation with 20 mL of 0.9% saline over one hour was followed by the administration of a 0.23% saline/5% glucose solution with 20 mmol/L KC1/L, resulting in gradual normalization of her fluid and electrolyte status.

The underlying cause of her deterioration was not identified until 18 hours after resuscitation had begun, when she passed the tip of the feeding tube. Radiologic examination confirmed that the tube had migrated through the small bowel, colon, and rectum without evidence of gastrointestinal perforation. Flushing the tube with normal saline confirmed that it was intact. The intact tube was expelled through the anus 12 hours later. There was no evidence of fluid, electrolyte, or renal dysfunction during a two-month follow-up period, nor was there evidence of subsequent gastrointestinal dysfunction.

Comment.—We believe that the use of adult-length nasogastric feeding tubes with weighted tips in pediatric centers is potentially hazardous and may increase the risk of diarrhea and hypernatremic dehydration with hyperosmolar feeds if gut peristalsis propels the weighted tip of the unnecessarily long tube through the bowel lumen. Careful attention to tube position is necessary when such tubes

are used in infants. The addition of length indicators, similar to those on infant-size endotracheal tubes, would aid surveillance and provide earlier evidence than roentgenograms of a migrating tube. Many of the complications associated with feeding infants enterally can be prevented by careful selection of the technique and materials used and by carefully monitoring tube position as well as the general physical and metabolic status of infants during hyperalimentation.

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Munchausen's Syndrome by Proxy and Video Surveillance

Sir-In their informative article in the October 1987 issue of AJDC describing various aspects of Munchausen's syndrome by proxy, Zitelli et al¹ made the statement, "Practices such as secretly going through mother's possessions, unannounced home visits,2 and concealed videotaping8 may be unacceptable to many professionals, difficult to carry out, and in some instances illegal [reference numbers changed]." We strongly disagree with the authors' inclusion of concealed videotaping (with reference to our 1983 articles) among unacceptable or illegal

practices. We also find such an inclusion surprising, since the authors emphasized the difficulty of achieving a favorable outcome in legal proceedings initiated to protect the child. Our decision to use hidden camera surveillance in this instance,3 and in subsequent cases,4 was based on the knowledge that a definitive diagnosis, supported by incontrovertible evidence, is crucial in such court proceedings. We believe that our primary obligation, as physicians, is to the patient and that no effort should be spared to determine the precise cause of the patient's condition in the most straightforward manner possible, while simultaneously minimizing additional risks. It is well established that children in this situation are at great risk for serious, often permanent, injury or death.

Critics of videotaping may forget that it is the patient (ie, the child) who is being watched secretly by the camera-not the mother. This distinction has been emphasized previously.67 Videotaping is performed solely for the child's benefit and protection and thus is clearly ethical. There is no question of "entrapment," since the presence of the surveillance apparatus in no way increases the likelihood that an illegal act will be committed. When conducted properly, the method is also perfectly legal, and the data obtained can be (and have been) used as convincing and unequivocal evidence in

legal proceedings. 8,4,7

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In Reply.—We appreciate the comments by Dr Frost and colleagues and the contributions they have made in the field of child abuse.

Covert videotaping of patients and their families indeed may be unacceptable to many professionals. Southall et al1 and others2 described in detail the extensive discussions they had with other professionals to address concerns before initiating videotaping. Epstein et al² expressed concerns about legal and ethical considerations and that the hospital has an obligation to provide privacy to patients and their families. They expanded the traditional role of patient observation to include covert video monitoring and took great pains to try to provide some element of privacy to the mother while she was in the patient's room. Epstein et al also openly expressed concern that the mother of their patient may bring suit against the hospital. Since the physician's primary responsibility was the care and protection of the patient, Epstein et al believed that covert video monitoring could be justified in their case but recommended that advice and cooperation of hospital administration, legal staff, and security were necessary before use. These same case reports also describe elaborate plans for concealing and even switching video cameras as well as monitors and providing 24-hour observers to watch the monitors. Some hospitals may not be able to provide such video and personnel support.

We believe that while covert video monitoring technically may be legal, it raises potentially serious ethical objections and is difficult to perform properly in many settings. However, we acknowledge that in extreme instances, when all other means of diagnosis have been exhausted, videotaping may provide incontrovertible evidence. Physicians must be wary, however, not to be overzealous and intrude on the parent's legal rights, such as secretly going through the mother's possessions.3 Rosen et al4 correctly stated that the approach to these patients must be individualized depending on specific details of the case as well as hospital resources. We strongly encourage that dealings with families be truthful and forthright, so that trust can be established and maintained to enhance habilitation of the family.

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Anaphylactic Shock due to Dacarbazine (NSC 45388)

Sir.—Dacarbazine, an imidazole carboxamide, has been used mainly in the treatment of malignant melanoma, sarcomas, and Hodgkin's disease.1,2 It has not been used as widely in the treatment of pediatric malignancies; however, the drug has been shown to be effective in the treatment of neuroblastoma.3 Adverse effects of this drug include anorexia, nausea, vomiting, bone marrow suppression, hepatotoxicity, an influenzalike syndrome, facial flushing and parasthesia, photosensitivity reactions, and veno-occlusive disease.4,5 To knowledge, hypersensitivity reactions have not been reported. We describe a child in whom anaphylactic shock developed while receiving dacarbazine infusion.

Patient Report.—The patient, a 3-year-old girl with widespread neuroblastoma, was hospitalized to receive chemotherapy consisting of cyclophosphamide (750 mg/m² intravenously [IV] once on day 1), vincristine (1.5 mg/m² IV on day 5), and dacarbazine (25 mg/m² one-hour IV infusion on days 1 through 5). She had no known allergies. The patient was noted to be sweating during the second day of the second course of this chemotherapy, during dacarbazine infusion. She was restless and

started to cry. The infusion was discontinued, and dacarbazine was not administered for the remainder of the cycle. Metoclopramide hydrochloride (Reglan) was the only other concomitant medication given to prevent nausea and vomiting. Two weeks later the patient received continuous infusion of etoposide for three days, as per the protocol. This drug was well tolerated. It was uncertain if the patient was allergic to dacarbazine; therefore, she was given the drug again during the next course. This time, however, the drug was administered in a very small dose (2 mg in 100 mL of saline) and very slowly. Within a few minutes of starting the infusion and after having received 5 mL of fluid, the patient developed respiratory distress, cyanosis, and a drop in blood pressure. The infusion was immediately stopped, and epinephrine and steroids were administered, resulting in immediate improvement. She also developed facial erythema that lasted for a few minutes. Recovery was complete. Dacarbazine has since been omitted from the patient's chemotherapy regimen.

Comment.—Hypersensitivity reactions to several antineoplastic drugs have been described,5 but no such reaction to dacarbazine has been reported, to our knowledge. The patient's first reaction to the drug was restlessness, cough, and crying. This subsided without any specific therapy a few minutes after the infusion was stopped. During the second cycle, however, the patient developed the typical anaphylactic reaction within few minutes of starting the low-dose infusion. This case highlights a new and potentially life-threatening reaction to dacarbazine.

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Further Comment on the Assessment of Bone Mineral Status in Children

Sir-In a recent reply letter in the May 1988 issue of AJDC, Drs Specker and Tsang' claimed that Dr Chesney and I provided spurious data regarding the radial bone mineral content of children at age 6 years.2 In fact, the values we provided were correct in grams per centimeter as opposed to the values in grams reported by Drs Specker and Tsang in their reply letter. By way of clarification, the values reported by Mazess and Cameron² were 0.486 g/cm and 0.475 g/cm for male and female children, respectively, whereas the value at age 6 years as reported by Specker et als in their original report was 0.356 g/cm. These are the values reported in our previous letter. It is unfortunate that Drs Specker and Tsang misread the table provided in the Mazess and Cameron article.

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Bone Mineral Content in Infants: Which Machine or Which Bone?

Sir.—We read with interest the article by Vyhmeister et al,¹ who measured bone mineral content (BMC) at the radial and humeral sites using the Norland 278A (Norland Corp, Fort Atkinson, Wis) photon absorptiometer.

The statement in the abstract that "We tested . . . photon absorptiometric bone density measurements . . . The humerus was a more reliable site of measurement" is misleading. The sentence refers only to the machine the authors used, and not to photon absorptiometry. The study shows only that the Norland 278A is not a very sensitive instrument, and not that the humerus is a more reliable site. Using a larger bone (the humerus), the authors obtained a coefficient of variation (7% for instrument-reading error) larger than that obtained by Greer et al² (3.9%) on the smaller radius site using the Lunar instrument (Lunar

Radiation Corp. Madison, Wis).

A potential danger of using an insensitive instrument to measure BMC is that it may not reveal clear BMC differences among groups in nutrition interventional studies, especially in short-term studies where small changes in BMC are expected to occur.

The authors might be reminded that an additional advantage of using the radius site is that it allows longitudinal studies into childhood, or even adulthood, because BMC norms used by most investigators have been developed at the radius site.

When a much more sensitive photon absorptiometry instrument exists for infants, it would appear appropriate to use the sensitive machine for clinical studies.

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In Reply.—In testing the humerus as a site for BMC measurements, we used the commercially available instrument we had (Norland 278A). We are therefore referring to measurements performed with a specific instrument. We have not performed the study using other instruments, but, as far as we know, this has not been done by others either. If the BMC at the humerus and radius sites were measured by another instrument (eg, Lunar instrument), we believe that our studies would be confirmed by the "more sensitive" instrument.

The coefficient of variation in our article referred to the variability of repositioning, together with the variability between two different investigators. This cannot be compared with the repositioning variability of one investigator, which was apparently the case in the article by Greer et al. In our studies, the coefficient of variation for the measurement, done by one investigator in the postmortem studies, was 3.6%, which is comparable with the findings of other authors using different instruments. (Variability in measurement of radius BMC reported by a group of six different

researchers at the Mead Johnson BMC Symposium, La Costa, Calif, December 1987 ranged from 4% to 7%.)

Although we agree that the Lunar instrument is more sensitive (capable of measuring lower BMC values), we do not agree that the instrument we used was an "insensitive instrument." The stated limit of detectability for the Lunar instrument is 0.03 g/cm, and we obtained measurements down to 0.034 g/cm in our patients.

The measurement of BMC is, at this point, mainly useful for serial studies. and the changes over time can be demonstrated either in the radius or the humerus. If the Norland instrument is used, the humerus should be the bone of choice in premature infants, or the low BMC of the radius will lead to a high rate of failure in obtaining the measurement. We agree that the advantage of using the radius as the measuring site is that most of the past studies were done on this bone. We do not believe that this should be the sole reason for selecting a particular method.

Instruments capable of measuring BMC are being improved frequently. and new machines are being developed. What most of the researchers have available this year will not be the state-of-the-art machine available in the near future. Because these instruments are expensive to replace, only a real difference in the limit of detectability or sensitivity (that would enable previously unattainable measurements to be made) would justify the purchase of new equipment. Meanwhile, we have demonstrated that the measurements of humerus BMC are reproducible and will allow researchers to do serial studies in 100% of premature infants. We have defined normal at-birth values for humerus BMC in infants at 24 to 42 weeks of gestational age, and we find that, in serial studies, the linear increase in humerus BMC is very comparable with that in previous studies of radius BMC. We argue that, regardless of the instrument used, the humerus site may be as good or better than the radius site simply because the humerus is larger.

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The Editorial Board Speaks . . .

Boyd W. Goetzman, MD, PhD





Boyd continues to be an extremely valuable member of our Editorial Board. He reviews in the area for which we receive the largest number of manuscripts, namely, neonatology/perinatology. Since we published his last biography, the following accomplishments have been noted: (1) Dr Goetzman has been elected to the Board of Directors of the California Perinatal Association; (2) he has been elected to the Executive Committee of the Perinatal Section of the American Academy of Pediatrics; (3) he is now the Program Chairman for the Perinatal Section's Program at the American Academy of Pediatrics Annual Meeting, held this year in San Francisco, from October 15 through 20. In addition, Boyd continues his educational and clinical care activities and has published and presented reports on brain damage in a contemporary neonatal intensive care unit population, on research in a lamb model for investigation of various basic aspects of hypoxemia, on research into the pulmonary circulation, and on the pharmacology of assisted ventilation and related conditions.

INNOVATION AND ADVANCES IN NEONATAL CARE

While the role of research in advancing the state of medical care is well established there must be another important factor. While we are waiting for the final research results crucial to the implementation of a new therapy such as surfactant replacement, medical care continues to improve. Our patients do better. Complications decrease and survival increases. Extrapolating from Richard Foster's ideas in Innovation: The Attacker's Advantage,1 the other important factor is probably innovation. By that I mean the introduction of new technology or improvement in existing or old methods by frontline people who believe that better care will be provided. This is in contrast to hypothesis-driven research, which is either systematically performed away from the clinical setting or with the primary care givers blinded to the treatment in question and with the goal of establishing a fact or principle.

Who is involved in this innovation and what are they doing? If we are fortunate, all of our frontline people are dedicated not only to providing care but to improving it. Physicians, nurses, respiratory therapists, ward clerks, pharmacists, and so on can be and are involved. Innovation occurs in neonatal intensive care centers where clinical research is infrequent and bench research is rare, as well as in our academic centers. Most often the innovations or changes introduced are small and mundane. However, many small changes when added together may produce a significant improvement. Of course, few of the changes turn out to be real improvements. Most are discarded immediately but others are true gems, improving care with little increase in cost and often at a savings.

Does it make a difference? I believe that it does. Much of neonatal care appears to have evolved through innovation. Mechanical ventilation, continuous positive airway pressure, parenteral nutrition, and even intravenous fluid administration are technologies that were borrowed from adult or pediatric medicine. Umbilical artery catheterization was an innovation. Infant transport equipment was assembled and continually improved by frontline people. The beautiful skin of our tiny premature infants is a credit to the nurses who tried emollients, created microenvironments, found tape substitutes, and kept alcohol off these infants' skin. The use of plastic cannulae to replace the scalp vein needles that replaced straight reusable needles

has also helped. Surgical examples are also easy to find. Double ligation and division of the patent ductus arteriosus by the transthoracic approach has given way to a single metal clip on the ductus applied by a retropleural approach. Often the procedure is performed in the neonatal intensive care unit, thus avoiding the stressful and personnel-intensive transport to the operating room. And so it goes, example after example that you can add to from your own experiences. When summed such changes have led to evolution of care patterns that provide for dramatic results such as the current survival of over 80% of infants weighing between 750 and 1000 g at birth.

Is innovation safe in the clinical setting, particularly if we encourage it, as Tom Peters suggests for other businesses in Thriving on Chaos?2 The reality is that innovation is going on and it is responsible for important advances in care. I believe that recognizing innovations and rewarding innovators will not only stimulate progress but will make the process of advancement safer for our patients. Innovation tends to be applied in the presence of low risk and where there is the ability to assess the effect of the change immediately. The important issue seems to be recognizing risks and switching to research techniques when appropriate. Innovations subsequently may become the subjects of clinical research to determine whether or not they are truly effective or safe. Perhaps development of ways to critique and disseminate important medical information that is not derived from research will help in this regard.

This is not a testimonial for uncontrolled clinical research or for a decrease in research of any type. To the contrary, I firmly believe that we need more and better research. It is an appeal to recognize the means by which we make advances in medical care and to encourage and facilitate all such endeavors. Technological advances are the key ingredient for innovation and they are coming rapidly, including computers, robots, new materials and devices, microelectronics, and biotechnology to name but a few. Thus, the future looks bright for our patients, who will benefit from the creative application of technology. It can and should be an exciting and satisfying time for everyone involved in health care provision.

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Leads From the MMWR

Morbidity and Mortality Report Centers for Disease Control, Atlanta

Recommendations of the Immunization Practices Advisory Committee Prevention of Perinatal Transmission of Hepatitis B Virus: Prenatal Screening of all Pregnant Women for Hepatitis B Surface Antigen

Infants born to mothers positive for hepatitis B surface antigen (HBsAg) and hepatitis B "e" antigen (HBeAg) have a 70%-90% chance of acquiring perinatal HBV infection, and 85%-90% of infected infants will become chronic HBV carriers.1.2 More than 25% of these carriers will die from primary hepatocellular carcinoma or cirrhosis of the liver.8 In the United States, an estimated 16,500 births occur to HBsAg-positive women each year (about 4,300 of whom are also HBeAgpositive), and approximately 3,500 of these infants become chronic HBV carriers. Prenatal screening of all pregnant women would identify those who are HBsAg- positive and thus would allow treatment of their newborns with hepatitis B immune globulin (HBIG) and hepatitis B (HB) vaccine, a regimen that is 85%-95% effective in preventing the development of the HBV chronic carrier state.2,4-6

In 1984, the Immunization Practices Advisory Committee (ACIP) recommended that pregnant women in certain groups at high risk for HBV infection be screened for HBsAg during a prenatal visit and, if found to be HBsAg-positive, that their newborns receive HBIG and HB vaccine at birth.7 Major problems have been encountered in implementing these recommendations. 8-12 These include 1) concerns about the sensitivity, specificity, and practicality of the current ACIP guidelines for identifying HBV carrier mothers; 2) lack of knowledge among prenatal health-care providers about the risks of perinatal transmis-

sion of HBV and about recommended screening and treatment procedures: 3) poor coordination among medicalcare workers who provide treatment and follow-up of mothers and infants: and 4) refusal of some public and private third-party payers to reimburse for HBV screening of pregnant women and treatment of their infants. In addition, concern has been expressed that these recommendations may not be practical or applicable in some U.S. jurisdictions where HBV infection is highly endemic, such as parts of Alaska and certain Pacific Islands.

Recent studies in several large inner-city hospitals, where all pregnant women were tested for HBsAg, have found that only about 35%-65% of HBsAg-positive mothers would have been identified by following the current ACIP guidelines. 8-12 In these studies, the prevalence of HBsAg in innercity black (0.4%-1.5%) and Hispanic women was higher than expected. Persons providing health care to pregnant women often are not aware of the risks of perinatal transmission of HBV and of the recommended screening and treatment guidelines.

Given these limitations, it is now evident that routine screening of all pregnant women is the only strategy that will provide acceptable control of perinatal transmission of HBV infection in the United States. Screening the approximately 3.5 million pregnant women per year for HBsAg would identify 16,500 positive women and allow treatment that would prevent about 3,500 infants from becoming

HBV carriers. Recent studies also indicate that the costs and benefits of universal testing of mothers are comparable to those encountered in other widely implemented programs of prenatal and blood-donor screening. 18,14 The cost of an HBsAg test ranges from an estimated \$3.50 per test in blood-bank laboratories to \$21.00 per test in private commercial laboratories. If one assumes an average screening cost ranging from \$12.00 to \$20.00 per test plus \$150.00 for the HBIG and vaccine needed to treat each infant of an HBsAg-positive mother, the cost to prevent one newborn infant from becoming a chronic HBV carrier would be between \$12,700 and \$20,700. HBsAg testing should be done early in pregnancy when other routine prenatal testing is done. The HBsAg test is widely available and can be added to the routine prenatal "panel" of tests without requiring additional patient visits. The advantages of making HBsAg testing routine during early pregnancy include 1) the ability to identify HBV carrier mothers that is not dependent on the health-care provider's identifying high-risk women or ordering HBsAg as a special test; 2) the availability of test results before delivery so that infants can receive HBIG and vaccine without delay after birth; and 3) appropriate counseling of families before delivery. 15 Because more than 90% of women found to be HBsAg-positive on routine screening will be HBV carriers, routine followup testing later in pregnancy is not necessary for the purpose of screening. In special situations, such as when the mother is thought to have acute hepatitis, when there has been a history of exposure to hepatitis, or when particularly high-risk behavior such as parenteral drug abuse has occurred during the pregnancy, an additional HBsAg test can be ordered during the third trimester. Few women in populations at low risk for HBV infection will have a change in HBsAg status during subsequent pregnancies. However, because of the expected benefits of making HBsAg testing a routine part of each prenatal panel, testing should be done during each pregnancy. Women who present for delivery without prenatal care or without medical records documenting the results of HBsAg screening should have the HBsAg test done as soon as possible after admission, since delay in administration of HBIG to infants of carrier mothers will decrease the efficacy of

therapy. In the studies that demonstrated the highest efficacy (85%-95%) of combined HBIG and HB vaccine prophylaxis, HBIG was administered within 2-12 hours after birth.2,4-6 In one study in which only HBIG was used for prophylaxis, no efficacy was found if HBIG were given more than 7 days after birth, and a significant decrease in efficacy was observed if it was given more than 48 hours after birth. 16 Only one-third of U.S. hospitals currently perform the HBsAg test as an in-house procedure, and many of these have technicians who are trained to do the test available on only one shift. Hospitals that cannot rapidly test for HBsAg should either develop this capability or arrange for testing to be done at a local laboratory or blood bank where test results can be obtained within 24 hours. The commercially available HBsAg tests have an extremely high sensitivity and specificity if positive tests are repeated and confirmed by neutralization as recommended by the manufacturers of the reagent kits. Testing for other markers of HBV infection, such as HBeAg, is not necessary for maternal screening. Mothers who are positive for both HBsAg and HBeAg have the highest likelihood of transmitting HBV to their newborns. However, infants of mothers who are HBsAgpositive but HBeAg-negative may become infected and develop severe, even fatal, fulminant hepatitis B during infancy.17,18 For this reason, HBIG and HB vaccine treatment of all babies born to HBsAg-positive women is recommended. HBsAg-positive mothers identified during screening may have HBV-related acute or chronic liver disease and should be evaluated by a physician. Identification of women who are HBV carriers through prenatal screening presents an opportunity to vaccinate susceptible household members and sexual partners of HBV carriers, as previously recommended.19 Screening and vaccination of susceptible contacts should be done by the family's pediatrician, primary health-care provider, or the physician evaluating the clinical status of the HBsAg-positive pregnant women. Implementation of the recommendations to prevent perinatal transmission requires maternal screening, treatment of the newborn in the hospital, and administration of subsequent doses of HB vaccine to the infant during pediatric visits at 1 and 6 months of age. Treatment failures due to lack of communication among health-care providers can occur, especially in situations where prenatal, obstetric, and pediatric care are provided in different facilities.20 Central coordination of the treatment of these infants by city. county, or state health departments would improve the education of the health-care providers involved and increase the likelihood that proper treat-

ment is provided.

In certain populations under U.S. jurisdiction, including Alaskan Natives and Pacific Islanders, as well as in many other parts of the world, HBV infection is highly endemic in the general population, and transmission occurs primarily during childhood.21 In such groups, universal vaccination of newborns with HB vaccine is recommended to prevent disease transmission both during the perinatal period and during childhood. Several studies have shown that HB vaccine given without HBIG will prevent 70%-85% of perinatal HBV infections and 95% of early childhood infections.22,23 In many of these areas with highly endemic HBV infection, prenatal screening is impractical because the population is isolated, laboratory facilities are not available, and/or health-care budgets and personnel are limited. In these areas, control of HBV infection can be better achieved by directing available resources into programs to vaccinate all children with HB vaccine. Programs for screening all mothers for HBsAg and providing HBIG to infants born to carrier mothers are costly and will add only modestly to disease prevention. They should be considered only after the program for universal vaccination of children has been implemented.

Recommendations

All pregnant women should be routinely tested for HBsAg during an early prenatal visit in each pregnancy. This testing should be done at the same time that other routine prenatal screening tests are ordered. In special situations, such as when acute hepatitis is suspected, when there has been a history of exposure to hepatitis, or when the mother has a particularly high-risk behavior such as intravenous drug abuse, an additional HBsAg test can be ordered later in the pregnancy.

If a woman has not been screened prenatally or if test results are not available at the time of admission for delivery, HBsAg testing should be done at the time of admission, or as soon as possible thereafter. If the mother is identified as HBsAg-positive more than 1 month after giving birth, the infant should first be tested for HBsAg; if negative, the infant should be treated with HBIG and HB vaccine. Hospitals where infants are delivered should have HBsAg testing capabilities or should be able to obtain HBsAg results within 24 hours from a local laboratory.

If a serum specimen is positive for HBsAg, the same specimen should be tested again, and then the test results should be confirmed by neutralization. It is unnecessary to test for other HBV markers during maternal screening, although HBsAg- positive mothers identified during screening may have HBV-related acute or chronic liver disease and should be evaluated by their physician. Infants born to HBsAg-positive mothers should receive HBIG (0.5 mL) intramuscularly (IM) once they're physiologically stable, preferably within 12 hours after birth. HB vaccine, either plasma-derived (10 ug per dose) or recombinant (5 ug per dose), should be administered IM in three doses of 0.5 mL each. The first dose should be given concurrently with HBIG but at a different site. If vaccine is not immediately available, the first dose can be given within 7 days after birth. The second and third doses should be given 1 month and 6 months after the first. Testing the infant for HBsAg and its antibody (anti-HBs) is recommended at 12-15 months of age to monitor the effectiveness of therapy. If HBsAg is not detectable and anti-HBs is present, the child can be considered protected. Testing for antibody to hepatitis B core antigen (anti-HBc) is not useful, since maternal anti-HBc can persist for more than a year. HBIG and HB vaccination do not interfere with the routine childhood immunizations.

Household members and sexual partners of HBV carriers identified through prenatal screening should be tested to determine susceptibility to HBV infection and, if susceptible, should receive HB vaccine. Screening and vaccination of susceptible contacts should be done by the family's pediatrician, primary health-care provider, or the physician evaluating the clinical status of the HBsAg-positive pregnant women. Obstetric and pediatric staff should be notified directly about HBsAg-positive mothers so that the neonate can receive therapy without

delay after birth and follow-up doses of vaccine can be given. Hospitals, as well as state, county, and city health departments, should establish programs to educate appropriate healthcare providers about perinatal transmission of HBV and its control through maternal screening, treatment of infants, and vaccination of susceptible household and sexual contacts of HBV carrier women. Programs to coordinate the activities of those providing prenatal care, hospital-based obstetrical services, and pediatric well-baby care must be established to assure proper follow-up and treatment of infants born to HBsAgpositive mothers and other susceptible household and sexual contacts. In populations under U.S. jurisdiction in which hepatitis B infection is highly endemic, including certain Alaskan Native and Pacific Island groups, vaccination of all newborns with HB vaccine is the most effective strategy for HB control. In these populations, such vaccination programs should be given highest priority. In areas where HBsAg screening of mothers and use of HBIG in infants born to HBV carrier mothers are not practical, the vaccination of all newborns with HB vaccine should be considered the appropriate treatment.

Editorial Note: Hepatitis B vaccine is the first human vaccine that can prevent both serious chronic disease and a uniformly fatal type of cancer. These recommendations, developed in consultation with representatives of the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, represent a major step toward control of perinatal hepatitis B transmission in the United States. Programs for universal screening of pregnant women are currently in progress in Hawaii, certain Canadian provinces, Italy, West Germany, New Zealand, Australia, and Japan. More extensive infant HB vaccination programs are in progress in Alaska. American Samoa, Korea, Taiwan.

Singapore, and the People's Republic of China. A number of U.S. healthcare facilities have already begun to screen all pregnant women for HBsAg.

State and local health departments can facilitate implementation of these recommendations by 1) working to assure that all women receiving prenatal care in both public and private sector programs are offered screening and appropriate treatment; 2) working to assure that costs of screening and treatment are covered by public and private third-party payers; 3) establishing programs to coordinate the transfer of information between prenatal, obstetric, and pediatric healthcare providers; and 4) providing health education about hepatitis B to the public and to health-care providers. CDC will continue to work with state and local health agencies and professional associations in hepatitis B prevention and control. (MMWR vol 37. No. 22)

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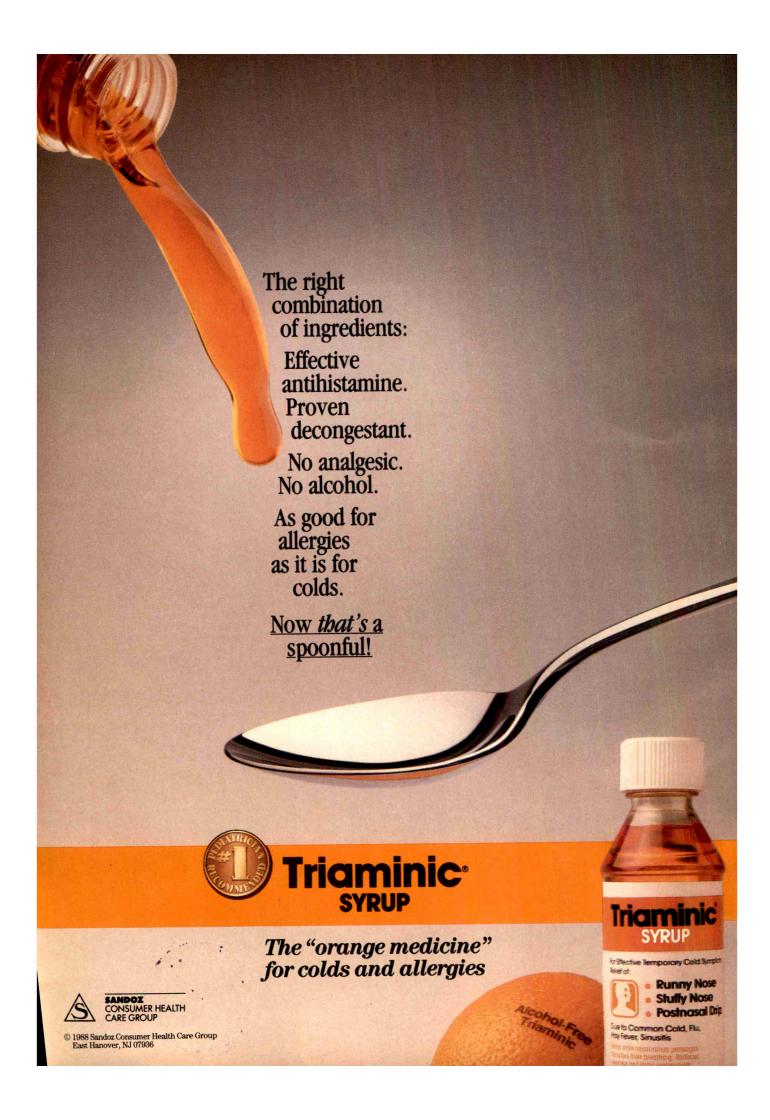
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Quotables:

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| 2-wk-2 yr** 2-3 yr 3-16 yr | 0.25 0.5 | 0 0.25 | 0 | |
| 3-16 yr | 1.0 | 0.5 | 0 | |

*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride Supplementation: Revised Dosage Schedule. Pediatrics 63(1):150-152, 1979.

**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula.

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Neurodevelopmental and Respiratory Outcome in Early Childhood After Human Surfactant Treatment

Yvonne E. Vaucher, MD; T. Allen Merritt, MD; Mikko Hallman, MD; Anna-Liisa Jarvenpaa, MD; Aimee M. Telsey, MD; Barbara L. Jones, RN, MN, CPNP

 We assessed postnatal growth, neurodevelopmental outcome, and occurrence of respiratory illnesses in 46 infants of very low birth weight who were enrolled in a randomized, controlled, bicenter clinical trial of human surfactant treatment for respiratory distress syndrome. No long-term adverse effects of human surfactant treatment were detected between control and human surfactant-treated infants with respect to growth, neurologic, or developmental outcome. Infants with chronic lung disease, regardless of treatment group, had poorer growth and were more likely to have neurodevelopmental abnormalities at 12 to 24 months of age.

(AJDC 1988;142:927-930)

In infants born long before term who either have established respiratory distress syndrome or who are at very high risk of developing this disorder. human surfactant treatment administered at birth has been accompanied by a substantial decrease in neonatal mortality, a decrease in pulmonary morbidities associated with both respiratory distress syndrome and conventional ventilation, and, in our prophylactic study,1,2 by a reduction in the occurrence of bronchopulmonary dysplasia. The question of whether this therapy improves mortality at the expense of increasing the rate of handicap, however, has not yet been adequately addressed. Furthermore. although immunologic sensitization is less likely with species-specific surfactant, the question has been raised

regarding the potential immunologic sensitization following administration into the airways of surfactant containing both the 35-kilodalton glycoprotein and the proteins of lower molecular weight that are found in human surfactant.³

Thus, as human surfactant and multiple heterologous surfactants are being evaluated for potential widespread use among neonatal populations, both their therapeutic efficacy and long-term safety must be established. The purpose of the present report is to describe the neurologic, developmental, and respiratory outcome in children who were enrolled as neonates in a randomized, controlled, bicenter trial of human surfactant therapy for respiratory distress syndrome.

PATIENTS AND METHODS

One hundred six premature infants of low birth weight with surfactant deficiency were enrolled between 1982 and 1985 in a bicenter (University of California Medical Center, San Diego, and Children's Hospital at the University of Helsinki), prospective. randomized, controlled trial of human surfactant therapy that has been fully described previously.1,2 In the first phase, human surfactant derived from human amniotic fluid was used to treat infants with established respiratory distress syndrome after the clinical, roentgenographic, and biochemical documentation of surfactant deficiency and respiratory distress syndrome accompanied by ventilatory failure within ten hours of birth (ie, "rescue" therapy). In the second phase we examined the efficacy of prophylactic surfactant administration at the time of delivery to infants at high risk for development of respiratory distress syndrome based on gestational age less than 30 weeks and lung maturity studies of amniotic fluid and/or tracheal or gastric aspirates indicative of lung immaturity (lecithin-sphingomyelin

ratio ≤2 and an absence of phosphatidylglycerol). As described in previous publications, 1.2 infants were excluded from the trial if there was evidence of lung maturity, clinical evidence of chorioamnionitis, or the presence of congenital abnormalities potentially affecting pulmonary development. The present follow-up study examined the neurodevelopmental outcome and the occurrence of respiratory illness in the surviving infants in each study group.

Infants who were randomized to control groups received a placebo injection of air from shielded syringes in an identical fashion as surfactant-treated infants. As infants in both surfactant trials were of similar birth weight and gestational age and were randomly assigned to surfactant treatment or control groups, all surfactant-treated infants in the present study were combined for purposes of data analysis and comparisons with the placebo-treated control group. No female predominance was noted in either the nursery or in the follow-up populations between surfactant-treated and control groups.

Neurodevelopmental follow-up in early childhood was prospectively obtained in 46 of 66 surviving infants with assessments scheduled at 6 to 8, 12, 18, and 24 months of adjusted and 36 and 48 months of chronologic age. Neurologic examinations were performed at 12 months using the Amiel-Tison neurologic screen. Developmental assessment used the Knobloch-Gesell Developmental Screening Inventory (n=6), the Bayley Scales of Infant Development (n=22), or the Griffith's scale (n=17), at 12 to 36 months of age and the Stanford-Binet (n = 1) test at 36 to 48 months of age. Length, weight, and head circumference were obtained at each clinic visit. Information was collected retrospectively at the time of neurodevelopmental follow-up on pulmonary sequelae and respiratory illness following discharge.

Results are reported as the mean \pm SEM. The Mann-Whitney U test was used to detect significant differences between groups. χ^2 Analysis was performed for com-

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| Growth and Development of Infants With and Without Bronchopulmonary Dysplasia (BPD)* | | | | | | | | | |
|--|--------------------|---------------------|--------------------------|------------------------|------------------------|------------------------------|----------|--------------|--------------|
| | | | | | Fronto-occipital | Developmental Scores§ | | | |
| Group | No. of Subjects | Birth Weight, g | Gestational Age, wk | Weight, Percentile† | Length, Percentile‡ | Circumference, Percentile | N | Mental | Motor |
| No BPD BPD | 28 15 | 971 ±52 963 ± 70 | 26.9 ± 0.4 27.9 ± 0.4 | 28±6 6±1 | 27±6 7±2 | 30±6 13±5 | 13 14 | 82±7 80±5 | 87±8 81±5 |

^{*}All values are the mean ± SEM.

Developmental scores are for infants at University of California, San Diego, and were obtained at a mean adjusted age of 18.1 ± 15 months.

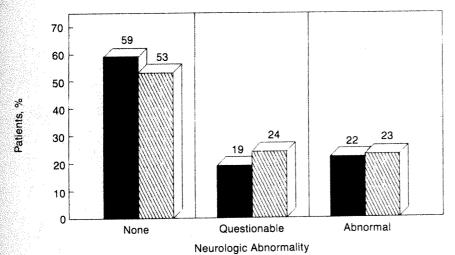


Fig 1.—Neurologic outcome at 12 months of adjusted age in surfactant-treated (solid bars) and control (shaded bars) infants. Questionable indicates abnormalities and/or asymmetry of motor tone; abnormal, cerebral palsy.

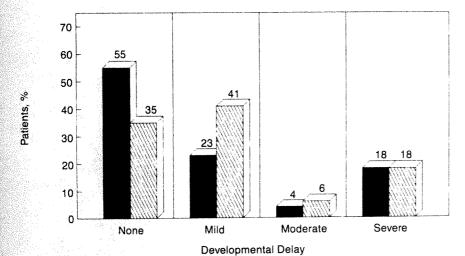


Fig 2.—Developmental outcome in surfactant-treated (solid bars) and control (shaded bars) infants at 20.7 ± 3.5 months (mean \pm SEM) of adjusted age. Developmental scores were graded according to age-adjusted test mean as follows: mild delay, between 1 or 2 SDs below mean; moderate delay, between 2 to 3 SDs below mean; and severe delay, more than 3 SDs below mean.

parison of incidence between groups. Since several different developmental examinations were used, results were compared using individual SDs from the population mean for the individual test. Only the single most recent test result for each child is included in the present report.

RESULTS

The 46 infants seen at neurodevelopmental follow-up included 28 infants treated with surfactant (rescue n=14, prophylactic n=14) and 18 control infants. All infants in Helsinki had universal access to pediatric care; only 4% became unavailable for followup. The San Diego population was much more mobile, had variable access to regular medical care, and was less likely to be available for follow-up during the entire period. Twenty-one percent (ten) of San Diego infants initially enrolled became unavailable for follow-up; five moved from the area and five failed to return for scheduled appointments. While these differences are important for purposes of study analysis, we have no reason to suspect that infants unavailable for follow-up represent a group of infants with a greater incidence of clinically significant neurodevelopmental handicaps. Thirty-nine infants (22 surfactanttreated, 17 control) were evaluated at 12 months of chronologic age or older, which represented 85% and 94% of enrolled San Diego and Helsinki infants, respectively. Outcome in both the Helsinki and San Diego groups was similar despite the differences in the rate of follow-up.

The birth weights and gestational ages were similar for both surfactanttreated and control groups (957 ± 57 vs 1010 ± 46 g, respectively, and 27.4 ± 0.3 and 27.2 ± 0.4 weeks, respectively). Mean chronologic and adjusted ages at the last examination were also similar (23.6 ± 3.5 months [range, 7 to 48 months] and 20.7 ± 3.5 months, respectively) for the entire group. Growth and neurodevelopmental and respiratory outcome results were similar for both prophylactic- and rescue surfactant-treated groups.

Respiratory Outcome

Sixteen (35%) of the 46 infants described in the present report (8/28 [29%] surfactant-treated; 8/18 [44%] controls; not significant) had roent-

[‡]P≤.005

genographic evidence of bronchopulmonary dysplasia (BPD) at 28 days of age, as defined by the grading scale of Toce et al. Seven infants required home oxygen and diuretic therapy for at least two months after discharge. Of these seven, one was given prophylactic surfactant, two received rescue surfactant treatment after respiratory distress syndrome was established, and four were control infants.

Information regarding the incidence of respiratory problems in the first two years after discharge was available for 43 of 46 infants. No differences were noted in the incidence of reactive airway disease or rehospitalization for pulmonary complications. Recurrent respiratory infection (≥3 episodes per year) occurred more frequently in children with BPD (63%) compared with those without BPD (48%). Recurrent respiratory infections were also more frequent in control (57%) compared with surfactant-treated infants (23%). Serum IgE levels were obtained between 9 and 12 months of age in seven surfactant-treated infants, all of which were normal ($<12 \mu g/L$).

Growth

Postnatal growth was similar in surfactant-treated and control groups. These extremely premature infants of very low birth weight remained smaller than average for adjusted age. 5 The mean of all growth measures for the entire study group was in the lowest quartile throughout the study period. A progressive trend toward "catch-up" growth was evident for all study infants between 24 and 36 months of age, with the mean weight, length, and head circumference at 24 to 36 months of age being 28%, 26%, and 29% months, respectively, compared with 11%, 15%, and 21% at 12 to 24 months. At the most recent evaluation, 43% of all infants had weights, 35% had lengths, and 37% had head circumferences that were in less than the fifth percentile for adjusted age. Infants with BPD were significantly lighter and shorter than those without roentgenographic evidence of chronic lung disease (Table).

Neurologic Outcome

The incidence and severity of intraventricular hemorrhage were not

significantly different in the surfactant-treated vs the control group. Seventy-one percent of surfactant-treated and 78% of control infants had intracranial hemorrhage detected by echoencephalography. Most hemorrhages were mild (grade I or II).6 Hemorrhagic ventricular distention or parenchymal involvement (grade III or IV) occurred in 21% of surfactant-treated and 34% of control infants. Posthemorrhagic hydrocephalus resulted in ventriculoperitoneal shunt placement in five surfactant-treated and three control infants. Periventricular cavitations (white-matter necrosis) were present on serial neonatal echoencephalograms in 22% of surfactanttreated and 25% of control infants.

No differences in neurologic outcome were noted at 12 months of adjusted age between surfactant-treated and control groups (Fig 1). Spastic cerebral palsy was present in nine children (four surfactant-treated, five control) at 12 to 24 months of adjusted age (diplegia, one; hemiplegia, two; quadriparesis, six). Although results of neurologic examinations in the first year were more likely to suggest or show abnormalities in infants with BPD (67% with BPD vs 40% without BPD), these differences were not significant.

Developmental Outcome

Nine of 39 infants examined at 12 months or more of adjusted age had moderate to severe developmental delay with developmental scores more than 2 SDs below the mean for the Knobloch-Gesell, Bayley, or Griffith's examination. Six of these nine infants had cerebral palsy. No significant differences were apparent in outcome between surfactant-treated and control groups (Fig 2). Infants with BPD had lower, but not significantly different, motor scores and were more likely to have developmental delay with a score less than 1 SD below the test mean for either mental or motor subsets (60% with BPD vs 50% without BPD; not significant) (Table).

COMMENT

Randomized, controlled, clinical trials of surfactant therapy using either a prophylactic strategy directed at infants who are high risk for respi-

ratory distress syndrome or rescue treatment for infants demonstrating roentgenographic and clinical evidence of respiratory distress syndrome generally have shown a decreased pulmonary morbidity with improved gas exchange in the first 72 hours after birth, a decreased frequency of extra-alveolar pulmonary air leaks (pneumothorax or pulmonary interstitial emphysema), and increased survival.7-11 No appreciable increase in other neonatal morbidities, including patent ductus arteriosus. necrotizing enterocolitis, infections, retinopathy of prematurity, or intraventricular hemorrhage, has been demonstrated using protein-containing surfactants. Although short-term morbidity has been reduced with surfactant treatment, the potential increases in long-term morbidity have not been resolved.

Our study demonstrates comparable neurologic and developmental outcome during early childhood in human surfactant-treated and control infants. Two previous studies also have reported improved short-term survival with similar neurodevelopmental outcome at 18 to 24 months in bovine or reconstituted bovine surfactant-treated and placebo-treated control infants. 12,18 Another study using low-dose artificial surfactant replacement likewise showed no long-term adverse effects. 14

The long-term neurodevelopmental outcome for preterm infants is compounded by a variety of medical, social, and parental factors. 15 While perinatal factors weigh heavily in predicting outcome in the first two years, 16-18 developmental outcome and school performance beyond 24 months of age are influenced primarily by educational and socioeconomic factors that operate in the child's environment. 19,20 Thus, it is not surprising that neurodevelopmental outcome in early childhood is similar for infants from both San Diego and Helsinki who had similar degrees of illness, birth weights, and gestational ages despite substantial differences in racial and socioeconomic population characteristics or availability of health resources. Differences in outcome related to educational and socioeconomic differences would be expected to become apparent in the preschool years. Continued follow-up is essential to determine whether surfactant-treated or control children will demonstrate later differences in the incidence of speech and language difficulties, attention-deficit disorder, or learning disabilities.

Bronchopulmonary dysplasia has been associated with an adverse effect on neurodevelopmental performance at 12 and 24 months. 21-24 In the present study, infants with BPD did demonstrate more neurologic and developmental abnormalities, but these differences were not statistically significant when compared with infants without roentgenographic manifestations of severe BPD. Since human surfactant therapy reduces the short-term morbidity associated with acute respiratory disease (ie, magnitude and duration of oxygen exposure and incidence of pulmonary air leaks), it might be

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expected that surfactant treatment should also reduce long-term neurodevelopmental morbidity insofar as adverse outcome is a consequence of severe chronic pulmonary disease. While the incidence of roentgenographic BPD at 30 days after birth was higher in control infants, a similar number of infants in each group had chronic lung disease of sufficient clinical severity to warrant oxygen and diuretic therapy after discharge. This finding suggests that factors other than the early ventilatory course are contributing to the pathogenesis of severe BPD and that the short-term efficacy of surfactant treatment may not result in a reduction in the longterm pulmonary or neurodevelopmental morbidity.

Strayer et al²⁵ were unable to document a decrease in levels of multiple components of the classic complement pathways, although antisurfactant immune complexes were detected in

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Quotables:

Art is long, and grants are but yearly.

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Perspectives in Biology and Medicine 1985

Sublingual Lorazepam in Childhood Serial Seizures

Jerome Y. Yager, MD, Shashi S. Seshia, MD

Sublingual lorazepam was successful in controlling serial seizures in ten children. There was both intrasubject and intersubject variability in the effective dose, which ranged from about 0.05 mg/kg to 0.15 mg/kg. Side effects were minimal and consisted of drowsiness, unsteadiness, nausea, and hyperactivity. Sublingual lorazepam is an easy and effective way to treat serial seizures at home.

(AJDC 1988;142:931-932)

Lorazepam, administered intravenously, is an effective treatment for childhood status epilepticus and serial seizures. ¹⁻³ A dose of 0.05 mg/kg to 0.1 mg/kg generally stops seizures; the dose can be repeated 15 minutes later if seizures continue or recur. ¹⁻³ Lorazepam can also be given rectally. ⁴ We have used lorazepam sublingually (SL) on an outpatient basis to treat serial seizures in ten children.

PATIENTS AND METHODS

All ten patients had intractable epilepsy and experienced bouts of serial seizures frequently. Bouts lasted 45 minutes to five days. Serial seizures often evolved into convulsive status epilepticus in five of the ten children. Serial seizures were defined as a series of seizures in which consciousness was regained between successive episodes.⁵

Parents (or other caregivers) were instructed to place the SL tablet(s) of lorazepam under the child's tongue between seizures. The initial dose was about 0.05 mg/kg. The dose was repeated 15 minutes later if there was no improvement,

if seizures recurred, or if the tablets were swallowed. The initial dosage was increased in subsequent attacks, if there had been no effect with the smaller dose, provided there were no side effects. Parents (or other caregivers) were asked to record the (1) onset and nature of the seizure bout, (2) dosage and time of administration, (3) latency of effect, (4) subsequent seizure frequency and severity, and (5) side effects, in the manner suggested by the Veteran's Administration Epilepsy Cooperative Study Group.6

A good response was defined as a cessation of subsequent seizures, and a partial response was defined as a reduction in the frequency or severity of seizures in a bout, when compared with the child's previous pattern of serial seizures.

RESULTS

A good response was obtained in eight patients and a partial response in two (Table). Patient 4 had a partial response to SL lorazepam during maintenance treatment with clonazepam. She had a good response once the clonazepam was discontinued and replaced by clobazam. None of the children had to be brought to a hospital

for additional treatment. Status epilepticus was not observed in any patient. Sublingual lorazepam dissolved within 20 s and was generally effective in 15 minutes.

Side effects were minimal and included drowsiness, unsteadiness, and nausea for up to one day, but the parents of six children attributed the drowsiness to seizures rather than to the drug. Two children became hyperactive for 24 hours after administration of SL lorazepam. None aspirated the tablets or experienced respiratory or cardiovascular disturbance. In all cases, the parents reported that the child's condition was better after treatment with SL lorazepam than after a bout of serial seizures that had been left untreated until the child was brought to the hospital. Two representative examples follow.

PATIENT REPORTS

PATIENT 1.—One patient, now 11 years old, began to have seizures at the age of 18 months. Bouts of serial seizures at three-week intervals developed at 8 years of age.

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| Patient/Age, y | Weight, kg | Seizure Type | Concomitant Therapy | Lorazepam Dose, mg | Latency, mir |
|----------------|------------|-----------------|------------------------|-----------------------|--------------|
| 1/12 | 30 | PCS | CZ, PH, VPA | 2-4 | 15-60 |
| 2/11.5 | 35 | Mixed | CZ, VPA | 1 | 15-60 |
| 3/17 | 40 | Mixed | CZ, VPA | 2 | 15 |
| 4/5.5 | 20 | PCS | CL, CB | 1-3 | 15-30† |
| 5/4 | 12 | Mixed | KD, PB, PH, VPA | 1-3 | 15-30 |
| 6/8.5 | 26 | Mixed | PH, PB, VPA | 2 | 60† |
| 7/13 | 25 | Mixed | PB, VPA | 1 | 15-30 |
| 8/1.2 | 8.5 | PCS | PB | 1 | 5-10 |
| 9/7 | 37 | Mixed | CZ, PB | 1 | 30-60 |
| 10/4.5 | 23 | Mixed | VPA, PB, PH, CB | 1-2 | 15-45 |

*PCS indicates partial complex seizures; CZ, carbamazepine; PH, phenytoin sodium; VPA, valproic acid; CL, clonazepam; CB, clobazam; KD, ketogenic diet; PB, phenobarbital sodium; and mixed, mixed seizures, which include generalized tonic-clonic, myoclonic, absence, drop, and partial.

†Partial response.

The bouts were stereotypical; for a day or two before such episodes, he would become hyperactive and sleep poorly. Seizures would then start without warning while he was awake or asleep. They would occur serially for up to three hours if left untreated, with each seizure lasting 30 to 90 s, recurring at intervals of one to five minutes during which consciousness was regained. Clinical phenomena during a full seizure included screeching, unresponsiveness, chewing movements, blinking, facial flushing, pupillary dilatation, vocalizing, stiffening of all limbs, and an attempt to sit up. These serial seizures were sometimes followed by convulsive status epilepticus. Sublingual lorazepam, in a dose of 2 mg after the first or second seizure in a bout, frequently aborted subsequent attacks, although 4 mg had to be given on some occasions. The effect of SL lorazepam was under video-electroencephalographic monitoring during a bout. Twenty clinical electrographically recorded seizures (ten with pupillary dilatation alone and ten full seizures as described) occurred during the first 28-minute period of recording. Lorazepam (2 mg) was then given SL, and the recording continued. He had one full seizure 11/2 minutes later and only nine brief clinical electrographic seizures (with pupillary dilatation alone) over the subsequent 15 minutes of recording. He had no further seizures.

PATIENT 2. - Patient 8, a 14-month-old female infant, had had seizures since the neonatal period. The seizures occurred every two to four weeks and were stereotypical; she began to stare and became hypotonic. She did not respond to visual, auditory, or painful stimuli. Ten to 15 minutes later, she developed generalized motor phenomena, either tonic-clonic or tonic. An entire episode lasted 35 to 45 minutes until terminated by diazepam or lorazepam given intravenously in the hospital. Pyridoxine treatment has been ineffective. An electroencephalographic recording during an episode confirmed the epileptic nature of the initial nonconvulsive phenomena, the subsequent generalization, and the effect of lorazepam.

Her seizures now stop within five to ten minutes after the administration of SL lorazepam at home. She has not had any episodes of generalization or status epilepticus since this form of treatment was instituted. The effect of SL lorazepam was confirmed by physician observation by one of us (S.S.S.) on one occasion.

COMMENT

Sublingual lorazepam was effective in controlling bouts of serial seizures

in all of our patients. A good response was obtained in eight and a partial response in two patients. None developed status epilepticus. The consistent response during several episodes in each case suggests that the effect was lorazepam related and not a chance association. Our patients were receiving concomitant treatment (Table) for intractable epilepsy. There is no information on the individual dosing requirement and pharmacokinetic behavior of lorazepam under this circumstance. The dose requirement for each child was, therefore, individualized, but there was also intrasubject variability in the dose required to control separate bouts. Thus, although 2 mg was generally adequate to control most of the bouts of patient 1, he required 4 mg on some occasions. Such variability also has been found with intravenous use.

Sublingual lorazepam is available in 0.5-mg, 1-mg, and 2-mg tablets. The SL tablets are distinct from the oral tablets. The average absorption half-life is 16 minutes when given sublingually compared with 55 minutes when given orally; the elimination half-lives are 11 hours and eight hours for the SL and oral routes, respectively. The substitute of the drug administered rectally.

Sublingual administration of lorazepam has several advantages: (1) it eliminates the often considerable delay that occurs when a child has to be brought to an acute care hospital for treatment; (2) the tablet can be given quickly and easily by parents, teachers, or other caregivers; (3) patients accept the tablet even if they are confused or combative (rectal administration may be particularly difficult in such cases or in older children); (4) medication error is minimized because of the fixed dose nature of the tablet (there is a greater potential for error with rectal use because a solution has to be made up for administration); and (5) the tablets can be given SL in any surrounding (the rectal solution cannot).

The incidence of serial seizures in patients with epilepsy is not known. They have been a troublesome problem in many of the children with intract-

able epilepsy treated by us. Serial seizures can also evolve into status epilepticus.5 The SL tablets disintegrate almost immediately and dissolve in about 20 s. Caregivers can generally use a finger to maintain the tablets under the tongue for this period, even in young children. The risk of aspiration is therefore small, particularly if the SL tablets are used between seizures in a bout of serial seizures or during prolonged nonconvulsive seizures. Lorazepam, given SL, may therefore be an effective, prompt, practical, and more acceptable alternative to rectally administered lorazepam for the home treatment of such seizures. The dose should be individualized because a number of factors are likely to cause intersubject and intrasubject variability. The SL route should not be used in those children with convulsive status epilepticus.

Our data on SL lorazepam, like those for the intravenous and rectal use of lorazepam in children, ¹⁻⁴ are based on "unblinded" observations. It may be practically difficult and ethically unacceptable, however, to do a blind trial in children with status epilepticus or serial seizures. In view of the small sample size, our findings should be considered tentative until confirmed by a study with larger numbers.

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Androgen Receptors in Boys With Isolated Bilateral Cryptorchidism

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 A study was conducted in boys with bilateral cryptorchidism, who were to undergo surgical orchiopexy, to determine if target-organ androgen insensitivity might play a role in the failure of the testes to descend into the scrotum. Nine boys older than 1 year in whom bilateral undescended testes was the only genitourinary abnormality were evaluated. Each subject was administered a six-week course of human chorionic gonadotropin (hCG), 3000 U/m² of body surface area, intramuscularly injected daily for five days and then twice per week. Basal and hCG-stimulated levels of testosterone were normal. However, hCG administration failed to induce testicular descent in all cases. At the time of surgery, scrotal skin and testicular biopsy specimens were obtained for propagation of cells in tissue culture. Androgen receptor levels and binding affinity were normal for the androgenspecific ligands dihydrotestosterone and metribolone in both skin fibroblasts and testicular cells. In addition, 5α -reductase activity was normal in scrotal skin fibroblasts. Nine boys with bilateral cryptorchidism and normal testicular androgen biosynthesis had normal androgen receptor-binding activity and 5α-reductase activity in cultured scrotal skin fibroblasts and testicular cells. Therefore, bilateral maldescent of the testes in these boys with cryptorchidism was not due to androgen insensitivitv.

(AJDC 1988;142:933-936)

Cryptorchidism is a common disorder of male sexual differentiation, 1-3 occurring in as many as 4.3% of newborn male infants (2.7% for full-term infants and 21% for premature infants). By 12 months of age, the incidence decreases to 1%, 4 with no further spontaneous migration of the testes occurring after that age. 5.6 Based on these data, 70% of undescended testes present at birth will descend into the scrotum during the first year of life. Unilateral cryptorchidism is twice as common (68%) as bilateral cryptorchidism (32%).7

In the male fetus, the testes descend during the eighth month of gestation. through the inguinal canal and into the scrotum, guided by the gubernaculum.8 Descent appears to be dependent on a series of mechanical factors, but it also involves the actions of androgens and possibly other humoral factors, such as müllerian inhibiting substance.8,9 In some infants with cryptorchidism, endocrine aberrations have been suggested by the findings of lower postnatal levels of plasma testosterone during the first four months of life, a reduction in the exogenous human chorionic gonadotropin (hCG) stimulation of testicular testosterone secretion, and decreased luteinizing hormone (LH) levels due to induction by luteinizing hormone releasing hormone (LH-RH). 7,10,11 However, the heterogeneity of the apparent causes of undescended testes is evidenced by the variability of these

responses among subjects. 7,10-14

The gubernaculum has been identified as an androgen target organ and a site of 5α-reductase activity in the rat¹⁵ and rabbit.¹⁶ The androgen-dependent epididymis is also intimately involved in testicular descent, and an anatomically abnormal epididymis occurs in some subjects with cryptorchidism.^{9,17}

Patients with androgen insensitivity have a variety of abnormalities, including testicular maldescent with inguinal testes but normal or elevated levels of plasma testosterone. 18,19 In light of the observations that testicular descent depends on androgen biosynthesis and target-organ responsiveness to androgens, we considered whether androgen insensitivity could lead to cryptorchidism in the absence of other abnormalities of sexual differentiation. Therefore, this study focused on the involvement of androgen receptors in cryptorchidism of boys who demonstrated a normal rise in plasma testosterone concentrations following hCG administration but who had nondescent of the testes.

SUBJECTS AND METHODS

All subjects were referred to one of us (J.P.G.), who performed the initial evaluation, operation, and follow-up examination. All subjects had normal physical appearance of the external genitalia at the time of referral except for the presence of bilateral undescended testes.

Materials

[1,2,4,5,6,7- 3 H]dihydrotestosterone (DHT) (5.0 × 10 2 MBq/mmol), [17 α -methyl- 3 H]metribolone (R1881) (3.2 × 10 2 MBq/mmol), [1,2,6,7- 3 H]testosterone (3.7 × 10 2 MBq/mmol), [4- 14 C]DHT (2.1 × 10- 3 MBq/mmol), and [4- 14 C] androstene-3,17-dione (2.1 × 10- 3 MBq/mmol) were obtained (New England

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Nuclear Corp, Boston) and purified by paper chromatography before use. Nonradioactive steroids, culture materials (GIBCO, Grand Island, NY, and MA Bioproducts, Walkersville, Md), fetal bovine serum (HyClone Laboratories, Logan, Utah), and other chemicals (Sigma Chemical Co, St Louis) were reagent grade or better.

Cell Culture

Scrotal skin and testicular tissue specimens were obtained at the time of surgical orchiectomy from eight boys between the ages of 10 and 36 months and from one 10year-old boy. For practical reasons, tissue from the gubernaculum, which is theoretically the primary tissue involved in testicular descent, could not be studied. Informed written consent was obtained according to institutional guidelines for clinical research. Fibroblast strains were propagated from tissue explants and maintained in minimal essential medium (MEM) with Earle's balanced salt solution supplemented with nonessential amino acids, pyruvate, glutamine, antibiotic-antimycotic, and 15% fetal bovine serum, as previously described.20

Hormonal Measurements

Luteinizing hormone and follicle-stimulating hormone (FSH) were measured in serum using LH and FSH radioimmuno-assay kits (Amerlex, Amersham Clinical Diagnostics, Chicago). Serum testosterone levels were determined following the protocol for a testosterone radioimmunoassay kit (Radioassay Systems Laboratories, Carson, Calif).

Androgen Receptor Assay

Specific binding of DHT and R1881 to the androgen receptors of cultured fibroblasts was measured, as previously described.20 Briefly, confluent fibroblast monolayers on 100-mm culture plates were incubated for 45 minutes at 37°C with tritiated DHT or tritiated R1881 (0.05 to 2.0 nmol/L) dissolved in MEM without fetal bovine serum. Metribolone (R1881) is a nonmetabolizable, synthetic androgen receptor ligand of high binding affinity that does not bind to serum proteins. After incubation, the medium was removed and an aliquot was counted to determine the free radioactivity. The cells were washed, scraped from the plates, collected by centrifugation, and assayed for androgen receptor binding by the dextran-gelatincharcoal method in cell lysates. By this method, free steroid is absorbed to an inert matrix in an unheated (0°C) and a heated (70°C for four minutes) aliquot and removed by centrifugation. Specific binding was calculated as the difference between the total binding (unheated aliquot) and the nonspecific binding (heated aliquot). The maximum binding capacity (Bmax) and the apparent dissociation constant (K_d) of the androgen receptor for DHT or R1881 were derived from Scatchard plots²¹ using linear regression analysis. Each 0.25-mL aliquot of the cell lysate contained 10 to 15 μ g of DNA, as determined by the method of Burton.²²

5α-reductase Assay

The method for quantitating the metabolism of testosterone, predominantly to 5α -reduced products, has been previously described.20 Briefly, fibroblast monolayers on 60-mm culture plates were incubated at 37°C with 4 mL of serum-free MEM containing 2 nmol/L (0.03 MBq) of tritiated testosterone with 198 nmol/L of nonradioactive testosterone. After 30 and 60 minutes, 0.5 mL of medium was removed and steroids were extracted into carbon tetrachloride along with 14C-steroid recovery standards; the steroid extracts were then dried and chromatographed. Silica gel thin-layer chromatography was used to separate and identify testosterone, androstenedione, and the following 5α -reduced steroids: 5α-androstane-3α,17β-diol and 5α -androstane- 3β , 17β -diol (androstanediols); DHT; androsterone; and 5α-androstane-3,17-dione. These areas were eluted from the silica gel and counted by liquid scintillation spectrometry. The quantity of 5α-reduced steroids formed from testosterone was calculated as the fraction of tritium radioactivity recovered in all 5α-reduced products multiplied by the total amount of testosterone in the medium as substrate. The 5α -reductase activity was expressed as picograms of 5α-reduced products generated per hour per microgram of cellular DNA.

RESULTS

Nine male subjects with bilaterally undescended testes, aged 1 year or older, were included in this study. Prior to bilateral inguinal orchiopexy, each subject was administered a sixweek course of hCG, 3000 U/m2 of body surface area, intramuscularly injected daily for five days and then twice per week. Basal testosterone concentrations in blood were below the level of detection (ie, <3.5 \(\mu\text{mol/L}\) in the eight subjects between the ages of 10 and 21 months and were 8.3 \(\mu\text{mol/L}\) and 14.2 \(\mu\text{mol/L}\) in the 3and 10-year-old boys, respectively (data not shown). 23,24 The LH and FSH levels measured before the administration of hCG were in the prepubertal range (data not shown). Following five days of hCG administration, plasma testosterone concentrations (mean [\pm SD], 186.5 \pm 143.2 μ mol/L; range, 70.0 to 570.7 μ mol/L) reached levels comparable to or greater than those of normal adult male subjects and were in the range reported previously to be normal in boys following hCG administration (mean, 120.3 \pm 55.8 μ mol/L; range, 63.1 to 234.0 μ mol/L).²³

The androgen receptor levels (Bmax) determined in the testicular and scrotal skin fibroblasts were similar, whether DHT (Table) or R1881 (data not shown) was used as the ligand. In some cases, tissue specimens were obtained from both the right and left testes. The androgen receptor binding was always similar when the two testes were compared. Similarly, the binding affinities (K_d) of the androgen receptors for the two different ligands were also normal. Furthermore, the Bmax and $K_{\scriptscriptstyle d}$ values from the cells of subjects were similar to those of normal newborn foreskin fibroblasts, except for one case (subject 6) with lower apparent binding affinity. However, qualitative tests of the androgen receptors of the scrotal skin fibroblasts from this subject were normal in temperature lability25 and up-regulation²⁶ experiments with R1881 (data not shown), suggesting that the altered binding affinity did not adversely affect the androgen receptor activity.

The mean 5α-reductase activity in scrotal skin fibroblasts of subjects with eryptorchidism (884 ± 319 picograms of product per microgram of DNA per hour) was in the same range as the 5\alpha-reductase activity in foreskin fibroblasts from normal subjects $(1067 \pm 667 \text{ picograms of product per})$ microgram of DNA per hour; n=27). Previous studies from our laboratory have shown that 5\alpha-reductase activity is undetectable in cultured testicular fibroblasts from subjects with a variety of abnormalities of sex differentiation despite the presence of activity in skin fibroblasts from the same individuals.27 Similar measurements were performed in only two strains of testicular cells from subjects with

Androgen Receptor Binding and 5∞-reductase Activity in Scrotal Skin and Testis Fibroblasts*

| | | | DHT Bir | nding | |
|----------------------------|--------------|-------------------|----------------------|------------------|--|
| Subject No. | Age, y/mo | Tissue | Bmax, fmol/mg DNA | K _a , | 5α-reductase Activity, pg Product/μg DNA/h |
| 1 | 0/10 | Testis Scrotal | 526 678 | 0.29 0.17 | 1641 |
| 2 | 1/0 | Testis Scrotal | 837 743 | 0.22 0.13 | 748 |
| 3 | 1/2 | Testis Scrotal | 540 836 | 0.23 0.15 | 431 |
| 4 | 1/3 | Testis Scrotal | 449 422 | 0.12 0.26 | 742 |
| 5 | 1/5 | Testis Scrotal | 919 427 | 0.43 0.17 | 797 |
| 6 | 1/7 | Testis Scrotal | 290 364 | 1.1 0.61 | 947 |
| **** (j. 1. å. 7 | 1/9 | Testis Scrotal | 413 550 | 0.18 0.12 | 892 |
| 8 | 3/0 | Testis Scrotal | 504 455 | 0.28 0.22 | 1093 |
| 9 | 10/0 | Testis Scrotal | 1687 549 | 0.24 0.21 | 663 |
| Controls (mean ± SD) | Newborn | Foreskin | 627 ± 173 | 0.29 ± 0.14 | 1067 ± 687 |

*DHT indicates dihydrotestosterone; Bmax, maximum binding capacity; and K_d , dissociation constant. All values for DHT binding and 5α -reductase activity are the mean of at least two independent determinations from successive subcultures. Binding of DHT in testis is expressed as the mean for both the right and left biopsy specimens. The 5α -reductase activity was measured only in scrotal skin fibroblasts, as described in the text.

cryptorchidism, and 5α -reductase activity was undetectable in both strains (data not shown). Therefore, further studies of 5α -reductase activity in testicular cells from subjects with cryptorchidism were thought to be uninformative and were not performed based on this experience and our previous work.²⁷

COMMENT

Despite the high frequency of cryptorchidism in male infants, relatively little is known about the mechanisms involved in testicular descent.9 It is generally agreed that testicular androgens, under the influence of the hypothalamic-pituitary axis, are involved. However, their exact role during the prenatal period is poorly defined. During the immediate postnatal period in male infants, there is a surge of testosterone that subsequently subsides gradually by about 6 months of age.24 During this same period of life, serum testosterone levels have been reported to be lower in boys with cryptorchidism than in boys with either normal or delayed spontaneous testicular descent. 7,10,11 This has led to

the hypothesis that cryptorchidism may be due to transient, functional insufficiency of the hypothalamic-pituitary-gonadal axis during fetal and early postnatal life. Basal and LH-RHstimulated LH values also have been found to be lower in some boys with cryptorchidism compared with those with normal or delayed spontaneous testicular descent.11 By contrast, others have found similarly elevated postnatal serum testosterone levels and augmented serum LH responses to LH-RH stimulation in normal male infants as in those with cryptorchidism. 12-14 Exogenous hCG, 28-80 testosterone,31 and gonadotropin-releasing hormone^{18,32-88} have all been used to promote postnatal testicular descent in boys with cryptorchidism. However, such therapy has met with variable success.

The gubernaculum has been suggested as the primary target tissue that responds to testosterone and promotes testicular descent. 8,9,15,16 The gubernaculum expresses 5α-reductase activity sufficient to convert testosterone to DHT and demonstrates significant morphologic changes in response

to androgens. 16 The gubernaculum has been proposed as a major participant in the mechanical process of testicular descent by maintaining traction on the testis.9,16 Direct measurements of the gubernaculum, both physically39,40 and biochemically, 16 have demonstrated that the gubernaculum is growing rapidly until the last stages of descent. when it finally undergoes regression. Other mechanical processes involving the progressive rise in intra-abdominal pressure from growth of the viscera or growth of the epididymis have been hypothesized as forces that push the testis through the inguinal canal. either in conjunction with the traction of the gubernaculum or totally independent of involvement of the gubernaculum.9,16 For practical reasons, the gubernaculum could not be included in the present studies and therefore we chose to use cultured genital skin and testicular fibroblasts as a model system for androgen action. 20,27

Our studies were designed to exclude those infants who might experience spontaneous testicular descent during the first six to 12 months of life; all subjects were older than 1 year at the time of orchiopexy. In addition, only cases of bilateral cryptorchidism were included since those with unilateral maldescent possessed the normally operative mechanism for descent in at least one testis.

Failure of the testes to descend. resulting from abnormal testicular testosterone biosynthesis, was precluded by the induction of normal plasma testosterone levels in response to hCG stimulation.23 One cannot, however, preclude that hypothalamic-pituitary interaction was normal or that the timing and coordination of the central nervous system-gonadal axis was appropriate for normal testicular descent during fetal life. Whereas subjects with partial and complete androgen insensitivity syndromes due to abnormal or deficient androgen receptors have disruption of testicular descent before or after entry to the inguinal canal,19 we did not observe any abnormalities in the androgen receptors in cells cultured from the testes or scrotal skin of infants with bilateral cryptorchidism. Therefore, we conclude that maldescent of the

testes in the present subjects was not due to androgen insensitivity.

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In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Gastrointestinal Arterial Fibromuscular Dysplasia of Childhood J. Todd Meredith, MD; Lizardo Cerezo, MD; Marcelino Alvarez, MD; George Price,

Gastrostomy Dependence in Two Constitutionally Short Children

Gunnar B. Stickler, MD

 We describe the medical odyssey of two infants who turned out to be constitutionally short. The measurements of length gradually came to rank below the fifth percentile during the first 18 months of life. Numerous tests were performed, and the diagnosis of gastroesophageal reflux led to fundoplication. The concept that higher energy intakes result in greater increases in length led eventually to gastrostomy. Increases in weight during gastrostomy feedings had no effect on growth in length. It was very difficult to convince the parents that the gastrostomies were not necessary. The parents had in fact become "gastrostomy dependent." The vague concept of "failure to thrive" proved to be misleading and obscured the knowledge that constitutionally short children can fall below the fifth percentile in length at any time before the age of 2 or 3 years.

The vague concept of "failure to thrive" may lead some physicians to the erroneous assumption that adequate food supply can overcome the slow growth of infants with constitutionally short stature. A misinterpretation of growth curves probably also leads at times to unnecessary concerns about the adequacy of weight gain.

(AJDC 1988;142:937-939)

We describe two short infants whose parents became "gastrostomy dependent." It is hoped that this report will help to avoid not only unnecessary placement of a gastrostomy but also morbidity associated with assessment and treatment of short stature and slow weight gain.

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PATIENT REPORTS

PATIENT 1.—The first patient, a boy, was born after 37 weeks of gestation. Some fetal distress before delivery led to a precipitate birth, but the Apgar score was 9. The patient's birth weight was 2.65 kg, and length was 48 cm. The infant was breastfed. At the age of 4 weeks he began to cough, and a diagnosis of pneumonia was made. It was also thought that he was gaining weight poorly, and he was placed on a regimen of infant formula. At the age of 3 months, again because of the "poor weight gain" and suspected milk protein allergy, he was given a soy-based formula. The patient was hospitalized in a major pediatric center, and gastroesophageal reflux was diagnosed by a pH probe study. This diagnosis eventually led to a Nissen fundoplication and a gastrostomy at the age of 6 months. There was occasional vomiting after this procedure; the patient's pediatrician thought that some of the vomiting was self-induced. Nevertheless, the patient was seen by an allergist. The skin test results were positive for milk protein, soy protein, chicken, house dust, and grass; immunotherapy with desensitization injections was begun.

The family history showed that the mother was 160 cm tall and the father was 167 cm, but one maternal aunt was 145 cm tall. The maternal grandmother was 152 cm tall, and the paternal grandmother's height was 157 cm.

When we saw the patient at age 19 months, his height was 75 cm and his weight was 9.6 kg. He looked well; if anything, his subcutaneous fat was more than adequate. He had a gastrostomy in place. The general physical examination produced completely normal results.

The patient was seen by our pediatric allergist and pulmonologist. Results of skin tests for house dust, timothy, and Alternaria were negative.

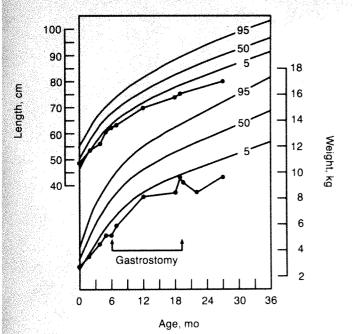
Our impression was that the patient was constitutionally short and did not require gastrostomy feedings. With considerable effort, the parents were convinced to clamp the gastrostomy and allow only oral feed-

ing. The weight of the patient promptly dropped during that period, as predicted, but eventually he began to eat. The gastrostomy was removed, and the patient continued to grow as outlined in Fig 1. He had no further vomiting or feeding difficul-

PATIENT 2.—The second patient, a girl, was the product of a normal term pregnancy, labor, and delivery. Her birth weight was 3.8 kg and her length was 52 cm. The infant was breast-fed and had no difficulties, but after the age of 2 months there was no further weight gain. She was breastfed "every 11/2 hours" and was given a prepared formula of cow's milk.

At the age of 31/2 months, the patient vomited occasionally and had not gained weight. Because of some coughing, a chest roentgenogram was obtained, which revealed some lower lobe infiltrates. The patient was treated with a combination of erythromycin ethylsuccinate and sulfisoxazole acetyl (Pediazole), and her condition seemed to improve. Milk allergy was suspected, and the patient was given a soybased formula. At age 4 months, because of fever, cough, another weight loss of 0.5 kg, and the impression that there was some perioral cyanosis, the patient was hospitalized in a children's medical center with the diagnosis of failure to thrive. Gastroesophageal reflux was noted. A diffuse bilateral infiltrate of the lungs was found, and aspiration pneumonia or bronchopneumonia was considered to be the diagnosis. Alveolar lung lavage revealed lipid-laden macrophages, which were consistent with, but not diagnostic of, aspiration of gastric contents, but the question of alveolar proteinosis was also raised. The patient received maintenance oxygen after dismissal, but the lung findings cleared quickly, and oxygen use was discontinued at home. Her weight gain, however, was interpreted to be inadequate.

Eventually, this poor weight gain led to rehospitalization. A lung biopsy specimen showed small-airway injury with peribronchial inflammation and fibrosis, changes considered to be nonspecific when the slide was reviewed by our pathologists. The



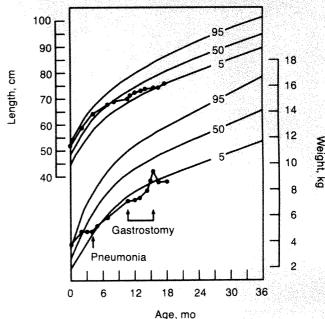


Fig 1.—Growth curve in patient 1. Numbers on curves indicate percentiles.

Fig 2.—Growth curve in patient 2. Numbers on curves indicate percentiles.

impression was formed that these changes were the result of either a small-airway injury, such as viral bronchiolitis, or aspiration.

At age 8 months, the patient's weight was 6.1 kg and the calculated oral intake was 2688 J. A nutritionist considered this intake to be inadequate. At the age of 10½ months, because of persistent gastroesophageal reflux, again documented by a pH probe, a Nissen fundoplication was done. At the same time, a gastrostomy was placed. While fed through this gastrostomy, the patient gained weight quickly but did not grow longer (Fig 2).

On our examination when the patient was 15 months of age, she was well developed and quite chubby. Her height was 74 cm (fifth percentile), and her weight was 9.4 kg (25th percentile). The pulse rate was 120 beats per minute, and respirations were 60/min. There was no cyanosis, and the chest was clear. The patient had abdominal distention, but there were no other abnormal physical findings. Oxygen saturation measured by ear oximeter was 91%. Respirations during sleep were 40/min.

It was decided that the gastrostomy was not necessary, and it was clamped. After five days, however, the parents were unable to accept this advice because the weight of the patient had dropped from 9.4 to 8.6 kg. The patient was hospitalized. Her swallowing mechanism was studied with barium and found to be normal. Her intake was monitored and found to be adequate for height. She did not lose any more weight.

At age 17½ months, she was eating normally, and the abdominal distention had disappeared when she was reexamined. Standing height was 74 cm, and the head circumference was 45 cm. All of her measurements were now in the fifth percentile. Respirations were normal.

The patient's maternal aunt was only 155 cm tall. The patient's grandmother was 165 cm, but the mother and father were 172 and 170 cm tall, respectively. The patient's mother remarked that her sister had never been a big eater. The parents have accepted the fact that the child is and always will be small.

COMMENT

The term failure to thrive continues to be used despite warnings that its use may lead to misunderstanding and even mismanagement.1 The constitutionally short child and the infant with central nervous system disease and microcephaly are two among many examples. Some physicians appear to be under the impression that (1) infants born at a certain percentile for height ought to stay in this percentile as long as they receive an adequate amount of energy intake and (2) more food gives infants better longitudinal growth or in some unknown way affects the genetically determined height.

Infants who turn out to be constitutionally short may have a length that

at birth is well within normal limits but that gradually drifts below the fifth percentile according to their genetic makeup. This may happen at any time during the first two or three years of life.^{2,3}

This growth phenomenon was documented by Smith et al.² They reminded us that birth length is related predominantly to maternal size and that length at 2 years of age correlates best with mean parental height.⁴ They observed that the downward "crossing" of percentile lines began after the first three to six months and that the new "channel" was reached at a mean age of 11.5 months. It also should be understood that growth charts provide only cross-sectional data, not "growth channel" information.

Even more important were the observations by Horner et al, who studied 149 children with constitutionally short stature. The growth deceleration was noticed between 3 and 6 months of age and was greatest in the first two years of life. By age 3 years, the children had a mean height more than 2 SDs below the mean for age. After this point, growth was parallel to that observed in normal children.

Tables of the "Fels Parent-Specific Standards for Height" might be helpful.4

Opitz and colleagues described

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another common misconception so well that they need to be quoted in detail:

As the pediatrician becomes aware of the growth curve 'falling off' the chart, he either has the child remeasured by the office nurse, who, not surprisingly, gets exactly the same or a slightly better value; or he measures the child himself and explains the observed discrepancy as still being compatible with a 'measurement error' or a 'moving target', or use of a different tape. But as the child's true growth potential becomes ever more evident, i.e. more accurately documented, the number of office visits and resulting anxiety and number of lab tests done increases until a consultant in the nearest secondary center may be asked how one goes about investigating growth hormone deficiency, or the Williams or Russel-Silver syndrome. By that time a sufficient number of lab tests have been done to have come up with at least one puzzling, abnormal result, and mother and child are so anxious as to present in a crisis condition. Since by now the child is following a rather steady rate beneath the third centile, the most important question to ask when beginning the evaluation is whether it is not more plausible to dash in the growth curve presently followed by the child backward to birth in this same channel and then to search all available records for evidence that the child had, in fact, been following that line all along from birth (rather than the probably fictitious one far above it created by kind office nurses). Normally such evidence is not found and leads to further disillusionment with the validity of most length measurements in early human life.

In our practice, we see with increasing frequency short infants considered to have failure to thrive. There seems to be a pattern: they undergo a multitude of diagnostic tests. Suspicions

are even raised that the parents are child abusers who are not providing enough food or love or both. In the absence of specific findings, these children are put through various feeding schemes. The mother may have been breast-feeding, and she is the first to be blamed for not having enough milk. The infant is given a prepared cow's milk formula, and when this does not work, milk allergy is suspected and the child is given a soy-based formula. If this switch does not lead anywhere. a pediatric gastroenterologist will find a gastroesophageal reflux, and sooner or later the child will have the famous fundoplication operation. There have been instances when proximal renal tubular acidosis was suspected, and the patient was given baking soda or fancier buffers.

This pattern is precisely what happened in our first patient. There should never have been any question that this was a constitutionally short child. Admittedly, to make this statement with certainty is easier in retrospect. However, if the heights of relatives had been considered from the very beginning, much harm could have been avoided.

The situation was a great deal more complicated in our second patient. This patient had serious pulmonary disease at the age of 4 months. It is not possible to reconstruct with accuracy what disease process it was. It may have been aspiration pneumonia or a rather severe bronchiolitis, a possibility suggested by a later lung biopsy specimen. There was spontaneous improvement after dismissal from the hospital, and the patient required

no further oxygen therapy. By this time, however, there was enough anxiety by physicians and the parents that the energy intake was suspected to be inadequate and related to a continuing lung process. In retrospect, the energy intake was normal for the patient's eventual size, but this miscalculation led eventually to the Nissen procedure and gastrostomy. It took this patient longer to reach the height curve she will most likely continue to follow.

Both patients experienced disproportional weight gains before the gastrostomy feedings were stopped. Yet, this weight gain had no influence on length, a result supporting the thesis that energy deficiency could not have had an influence on longitudinal growth. However, both sets of parents were extremely concerned about the need for the gastrostomy as a port of entry for, as it turned out to be, an excessive energy intake. A great deal of reassurance and even hospitalization were necessary before they could be convinced that the child would not starve.

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In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Childhood Fibrous Tumor With Psammona Bodies: Clinicopathologic Features in Two Cases

Nancy S. Rosenthal, MD, Fadi W. Abdul-Karim, MD (Arch Pathol Lab Med 1988;112: 798-800)

Determination of Fitness in Children With Asthma

Use of Standardized Tests for Functional Endurance, Body Fat Composition, Flexibility, and Abdominal Strength

Robert C. Strunk, MD; Diane Rubin, TRS; Laura Kelly, TRS; Bobby Sherman, TRS; Jolene Fukuhara

 Children with asthma frequently have exercise-induced disease that can limit their participation in both organized sports and vigorous free play. We measured fitness in a group of children with moderately severe to severe asthma with an instrument that is used widely and is available to clinicians for assessment of the physical capability of their patients. Abnormalities in physical fitness were present primarily in the area of endurance, with performance in the nine-minute run frequently found to be low. Increased skin-fold thickness was also present more frequently than in the normal population. Abdominal strength and flexibility were normal. Abnormalities in fitness were not well explained by measures indicating the presence of poorly controlled disease. All children with significant asthma probably should be tested to document the level of fitness so that appropriate intervention can be

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Children with asthma frequently have exercise-induced asthma (EIA), which can limit their participation in both organized sports and vigorous free play. 1.2 Several studies have demonstrated that patients with asthma can improve their exercise performance after participating in one of a number of physical conditioning programs. 3.8 Because swimming is less

frequently associated with EIA than is free running, most exercise programs have focused on swimming exercises, although patients with severe asthma can participate without adverse effects in training programs consisting of long-distance running. 4.8

Neither of the studies on running in patients with asthma4,8 compared the level of functioning in patients with normal values. Thus, the investigators were unable to determine degrees of abnormalities before the conditioning program was started or to determine if the improvements achieved during training allowed the patients to reach the normal range. Ludwick et al9 used standardized bicycle ergometry to define the level of fitness of a group of children with severe asthma and to document the effect of a physical rehabilitation program on fitness. While the testing of fitness by bicycle ergometry is easy and safe, the equipment needed for the testing is relatively expensive and is not widely available to clinicians. The purpose of the present study was to determine fitness of a group of children with moderately severe to severe asthma using the American Alliance of Health, Physical Education, Recreation and Dance Fitness Test Related Health (HRFT),10,11 a measure of fitness that is used widely and is available to clinicians both for assessment of the physical capability of their patients and for documentation of the effectiveness of rehabilitation programs.

SUBJECTS AND METHODS Subjects

The sample consisted of 76 children and adolescents admitted consecutively to the pediatric inpatient units of the National

Jewish Center for Immunology and Respiratory Medicine, Denver, who met the following criteria: (1) a primary diagnosis of asthma according to the criteria established by the American Thoracic Society12; (2) 9 to 17 years of age; and (3) successful completion of the HRFT within two weeks of admission so that the results reflected fitness levels before admission. Successful completion of the HRFT was dependent on completion of all four tests with a good effort and without asthma. The patients had been referred for asthma that had been difficult to control in their home communities; poor control of asthma was evidenced by frequent histories of respiratory failure (22% of the children) and seizures during asthma attacks (13%), a need for oral steroid medication to control symptoms (99%), and frequent use of medical services for asthma in the preceding year (mean numbers of hospitalizations and emergency department visits for asthma in the preceding year were 2.4 and 5.2. respectively) (Table 1). In general, patients' symptoms were well controlled at the time of admission as evidenced by the relatively normal pulmonary functions (Table 1). The good control was often achieved by large increases in dosages of steroid medication in the weeks before admission. Asthmatic characteristics documented in the children are listed in Table 1. There were 42 boys and 34 girls, with a median age of 13 years (range, 9 to 17 years). Parents gave consent for participation of their child in the study. The study design and consent form were approved by the National Jewish Institutional Review Board.

HRFT

The HRFT consists of four subtests: (1) abdominal strength, measured by the number of sit-ups completed in 60 s; (2) flexibility, measured by the distance reached toward one's toes while sitting on the floor with outstretched legs; (3) body fat composition, measured by skin-fold thickness

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| Table 1.—Characteristics of the 76 Patients | |
|--|-------------|
| Characteristic | Patients, % |
| Disease duration >8 y | 66 |
| History of respiratory failure | 22 |
| History of seizures during asthma attacks | 13 |
| Steroid use in year before admission | |
| None | 1 |
| Episodic use | 54 |
| Continuous use every other day or daily | 45 |
| History of exercise-induced bronchospasm | 93 |
| Medications on admission | • |
| Theophylline | 94 |
| β-Agonists: | |
| Oral | 53 |
| Inhaled | 89 |
| Steroids | |
| Oral* | 76 |
| Inhaled | 25 |
| Pulmonary functions on admission | |
| Forced expiratory volume in 1 s | |
| <80% predicted | 15 |
| Forced expiratory volume from 25%-75% | |
| vital capacity <70% predicted | 73 |
| Thoracic gas volume >120% predicted | 62 |
| Specific airways conductance <70% predicted | 32 |
| Socioeconomic status of parents | UL |
| Major business and professional | 13 |
| Medium business, minor professional, technical | 51 |
| Skilled craftsman, clerical, sales workers | 20 |
| Machine operators, semiskilled workers | 12 |
| Unskilled laborers, menial service workers | 4 |
| Medical services use in the year preceding admission (mean ± SD) | ~ |
| Hospitalizations | 2.4 ± 3.1 |
| Emergency department visits | 5.2±8.9 |
| Physician office visits for treatment of asthma | 7.2 ± 7.6 |

^{*}Mean daily steroid dose on admission, 17 mg of prednisone.

at the triceps and subscapular sites using a Lange caliper for which the test was calibrated; and (4) functional endurance, measured by the distance covered in a nineminute run. The HRFT has been standardized by testing of 10000 normal children nationwide. 10,11 Percentile scores have been determined for each age to facilitate sameage group comparisons. In a normal population 25% of subjects would fall into each of the four quartiles. A score lower than the 25th percentile is considered poor, 25% to 49% is fair, 50% to 74% is good, and 75% or higher is excellent. 10,11 For abdominal strength, flexibility, and distance run, poor results were given low percentile scores; increased skin-fold thickness, reflecting too much body fat, was given a low score.

To minimize the potentially subjective aspects of the test, several precautions were taken to standardize its administration and interpretation. These measures assured, as much as possible, that results of the tests reflected fitness and were not limited by either EIA or a suboptimal effort. Administration of all prescribed asthma medication, including bronchodilators used immediately before exercise, was continued to reduce the possibility that asthma would limit performance in the tasks. Physicians were immediately available for treatment of EIA or other physical

problems that might occur because of exercise testing. Testing sessions all took place at the same time of day and were each administered by two staff members from the recreational therapy and physical education department (RT/PE). Only six staff members administered all of the tests; these personnel were thoroughly trained in the testing procedures described in the test manual.

Because the nine-minute run subtest is particularly effort dependent, two measures were used to determine the validity of the score, that is, to document that a subject gave a good effort. First, heart rates were measured before and immediately after the functional endurance subtest. Second, a motivation checklist was devised by the RT/PE staff (available from R.C.S. or the RT/PE staff). This checklist consisted of five questions to assess behaviors and verbalizations before, during, and after the nine-minute run. From these answers the staff members determined whether the effort was good or not. The checklist was completed by both staff members. Interrater reliability among observers was established at 85% or better. The effort was not considered valid unless the patient had a heart rate of at least 75% of the predicted maximal heart rate for age at the end of the exercise period13 and both

staff members considered that the patient had good motivation during the test.

Other Variables

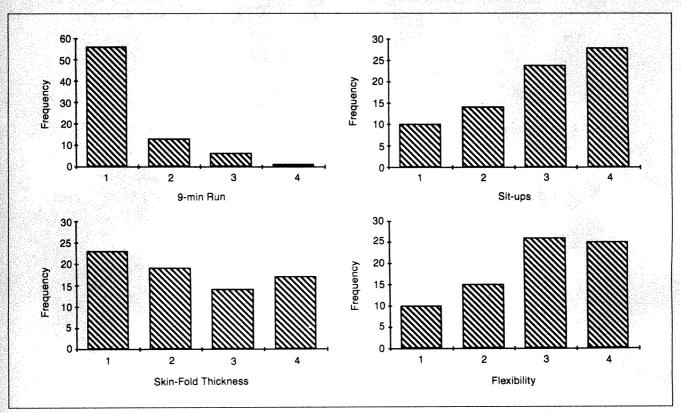
Medical variables were obtained from referring physicians' records or the admission history. Pulmonary function tests were performed using standardized methods in the Pulmonary Physiology Unit at the National Jewish Center for Immunology and Respiratory Medicine.14 Numbers of hospitalizations, emergency department visits, and physician office visits for treatment of asthma were confirmed by calling all of the possible care providers identified by the parents and referring physician(s). Analyses of the medical services-use data were done using a composite score in which types of use were assigned weights based on their relative costs (hospital day = 8.5, emergency department visit = 3, and physician office visit = 1). The family's socioeconomic status was determined on the Hollingshead Scale. The score is based on the type of occupation and level of education of the working parent(s).15

Data Collection

All of the data were collected prospectively. On admission each child was scheduled for HRFT to evaluate physical fitness (done during the first two weeks of hospitalization) and to undergo pulmonary function testing (done within the first 24 hours of admission). One hundred three consecutive admissions were eligible for the study. Twenty-seven patients were excluded from the study because the nine-minute run subtest was not completed within the first two weeks for the following reasons: EIA, 17 patients; knee pain, one patient; and poor effort on the HRFT, nine patients. None of the 17 patients with EIA during the nine-minute run required more than inhaled bronchodilators to control their EIA. There were no other medical complications of the testing. Preliminary analyses indicated that the 27 patients excluded from the study were not different from the remaining 76 patients in any of the criteria listed in Table 1. In addition, patients with poor effort did not have any more psychologic problems, as determined during interviews by social workers on admission. Data for determination of the socioeconomic status were collected during intake by the nurses and social workers.

Physical Fitness Program

All subjects were required to attend several activities on a weekly basis. These included physical education four times a week with primary emphasis on sports and



Frequency distributions of results of four subtests of Health Related Fitness Test in 76 patients. Results expressed as number of patients in each quartile. 1 indicates <25th percentile (poor fitness); 2, 25th to 49th percentile (fair), three, 50th to 74th percentile (good); and 4, >74th percentile (excellent). In a normal population 25% of children would be expected to be in each category; therefore, if this sample of asthmatics had normal levels of fitness, 19 patients would be in each of four categories.

motor skills appropriate for the child's developmental age and aerobic conditioning three times per week for 60 minutes each. A number of team sports and intramural activities were available to patients as well, but attendance was not mandatory.

During the period of training, treatment for asthma was adjusted to ensure maximal clinical functioning. Because increases in cardiopulmonary endurance observed during the training may have been related to improvements in pulmonary functions, all spirometry values obtained before administration of inhaled bronchodilator therapy were averaged for the three-day intervals around the initial and final testing days. Mean values of forced expiratory volume in 1 s (FEV₁) greater than 80% of the value predicted for the child's age, height, and sex were considered normal.

Statistical Analyses

For these analyses the results of the nine-minute run and skin-fold thickness subtests were used as dependent variables; these variables were entered in the analyses as percentile scores. Sit-ups and reach were not used because the results of these subtests were normal. The following 11 independent variables were considered: steroid use in the year before admission, steroid dose on admission, history of respiratory failure and/or hypoxic seizures, medical services use in the year before admission, pulmonary function on admission (FEV₁, forced expiratory volume from 25% to 75% of vital capacity, thoracic gas volume, and specific airways conductance), length of disease, histories of EIA and recent exacerbations of disease, and socioeconomic status. The independent variables were entered sequentially into a regression analysis to assess their effect on the dependent variables.16 Since these variables were not independent of one another, the order that variables entered into the analysis would affect the judgment of how important a particular variable was. The variables were entered in a stepwise fashion in the order listed above. If the variable entered at a significant level, then it was retained in the analysis. Subsequent variables were retained in the analysis only if they added significant information beyond the variables already retained in the analysis.

RESULTS Fitness on Admission to the Program

The results of the initial tests are shown in the Figure. Performance in the functional endurance or nine-minute run subtest was frequently low, with 91% of the children performing at or below the 50th percentile (compared with the expected 50% of a normal population): 74% had scores at or below the 25th percentile and 51% of the children had scores at or below the tenth percentile. These results were different from those in the normal population since the 95% confidence interval of $91\% \pm 7\%$ for the percentage of children performing below the 50th percentile did not include the 50th percentile. The children also had increased skin-fold thickness more frequently than the normal population. Although the overall distribution of skin-fold thickness results was not different than that in the

normal population (58% ≤50th percentile with a 95% confidence interval of $58\% \pm 11\%$; $32\% \leq 25$ th percentile with a 95% confidence interval $32\% \pm 10\%$), the results were skewed toward large increases in skin-fold thickness with 21% of subjects at or below the tenth percentile (95% confidence interval of $21\% \pm 9\%$). Poor performance in the nine-minute run was significantly correlated with increased skin-fold thickness (r=.54,P = .0001). Results of the abdominal strength and flexibility subtests were normal, with only 13% of subjects in the 25th percentile or less for each group.

Associations Between the Levels of Fitness and Criteria Used to Define Severity of Asthma

For the nine-minute run, only steroid use in the year before testing was significantly related to the variability in the results (P=.0004). However, only 13% of the variability in the results was explained. Addition of the remaining ten variables explained only an additional 14% of the variability, for a total of 27%.

For the skin-fold thickness, steroid use (P = .01), FEV, (P = .02), and thoracic gas volume (P = .007) explained 23% of the variability. Addition of the remaining eight variables explained only an additional 10% of the variability, for a total of only 33%. Socioeconomic status was not significantly associated with either the nine-minute run or the skin-fold thickness and did not improve the variability in the stepwise regression analyses. (Directions of correlations with steroid use are as follows: nine-minute run, more use was associated with lower scores; skinfold thickness, more use was associated with lower scores; FEV, worse flows were associated with lower scores; and thoracic gas volume, better volumes were associated with lower scores.)

Fitness Levels After Participation in the Rehabilitation Program

The HRFT was done at four-week intervals during the hospitalization and at discharge. Fifty-eight patients had a valid test shortly before discharge, with the interval between admission and discharge ranging from one to 11 months (median, three

Table 2.—Changes in the Results of Subtests of the Health Related Fitness Test
After Participation in a Physical Rehabilitation Program*

| | Mean (±S | D) Percentile | |
|---------------------|------------|---------------|------|
| Subtest | First Test | Second Test | P |
| 9-min run | 19±21 | 29 ± 22 | .003 |
| Skin-fold thickness | 42 ± 30 | 38 ± 29 | .55 |
| Sit-ups | 62 ± 27 | 73±24 | .004 |
| Flexibility | 58 ± 20 | 64 ± 26 | .007 |

*Data for a second test were available for 58 of the 76 patients tested initially. P values are for Wilcoxon's sign-rank tests comparing the means for first and second tests. Data are presented as the mean \pm SD only for the 58 patients who were retested before discharge.

months). The most common reason for the study not being repeated before discharge in the other 18 patients was difficulty in scheduling the test during discharge procedures. Initial scores on the HRFT and criteria for severity of asthma in those 18 patients were similar to values in the 58 patients who underwent testing before discharge.

By the time of discharge, the scores in the nine-minute run and sit-ups and reach tests had all improved significantly, but skin-fold thickness had not changed (Table 2). For the nine-minute run, 43 of 58 subjects had improvements of at least 10% in the distance run

The results of the nine-minute run might have been improved because of real training during the rehabilitation or they may have been influenced positively by improvements in control of the asthma or reduction of the steroid medication dosage. We examined the effect of overall control of asthma on the differences in the results of the nine-minute run by examining results of spirometry testing at the three-day intervals around the initial and final tests. These results were available in 48 of the 58 children who were retested before discharge. Three groups were identified. Thirty-four children had normal values in both three-day intervals; nine children had abnormal values initially but their values were normal at the time of the final testing; and five children had abnormal values at time of the final testing. Increases in the percentiles for the nine-minute run scores were not significantly different for the three groups (mean \pm SD increases in nine-minute run percentiles were $16.4\% \pm 18.2\%$, $8.1\% \pm$ 14.9%, and $19.0\% \pm 14.2\%$, respectively). The dosage of oral steroid

medication was reduced an average of 75% in the 50 patients who were receiving this drug on admission. However, there was no significant relationship between the increases in distance run and the decreases in steroid dosage (r=.00, P=.89).

COMMENT

The present study demonstrates that abnormalities in physical fitness among patients with moderately severe to severe asthma are present primarily in the area of endurance. The nine-minute run is extremely effort dependent, but several precautions ensured that an abnormal result reflected fitness of the patient and not simply a poor effort. Results of the sit-up and reach tests, both of which also required effort, were normal. Abnormalities in skin-fold thickness were also more frequent than in the normal population, but not as frequent as abnormalities in the nine-minute run. As expected, poor skin-fold thickness was significantly correlated with poor performance in the nine-minute run.

The absence of a correlation between the levels of fitness and measures indicating the presence of poorly controlled disease suggests that the basis for patients with asthma not having good fitness is multifactorial, involving more than just severe disease. Since many children with asthma are encouraged to exercise by their primary care physicians, their parents, or their schoolteachers to prevent wheezing, it is possible that the lack of endurance demonstrated in the nine-minute run is simply due to a lack of conditioning.

Steroid use, which correlated with results of both functional endurance and skin-fold thickness, may also have played a role in development of abnormal fitness. Steroids are known to increase body fat composition, causing the characteristic cushingoid habitus.17 Steroids can also produce a myopathy with reduction in proximal muscle strength17 that could contribute to the lower functional endurance. However, improvements in fitness did not correlate with reductions in steroid dosages. Therefore, it seems unlikely that steroids played a primary causative role in the development of the original abnormalities in fitness.

The results of the nine-minute run and skin-fold thickness tests may not have been well explained by the medical variables because of the relatively homogeneous nature of the sample: most of the patients had a history of EIA, had had asthma for many years, and had experienced exacerbation of their disease in the year before testing. However, the patients were not homogeneous for a measure of the most severe asthma, a history of respiratory failure or hypoxic seizures, and the amount of medical services use in the year before testing. Surprisingly, neither a history of respiratory failure/hypoxic seizures nor medical services use were associated with

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fitness.

Participation of these children in a multifaceted physical rehabilitation program was associated with improvements in three of the four areas of the HRFT, with increases of 52% in the nine-minute run, 18% in sit-ups, and 10% in reach. The changes in the nineminute run were greater than those observed in the studies of the running training programs for asthma reported by Nickerson et al' and Fitch et al,8 who documented improvements of 13% in the distance run in 12 minutes and 11% in maximal oxygen consumption, respectively. The greater improvement in subjects in our study may be due to the intensity and length of our rehabilitation program. The program used by Nickerson et al was as intense as ours (four times a week) but much shorter (only six weeks). The program used by Fitch et als was as long as our program (three months) but was less intense because the patients were outpatients and attendance was only 68% of possible sessions attended. Even though the changes in functional endurance were significant, the scores in the nineminute run tests were relatively resistant to change, improving from a mean in the 19th percentile to only the 29th percentile. The skin-fold thickness did not improve at all. Correction of abnormalities of the degree present in our children apparently requires longterm rehabilitation.

Monitoring fitness and providing intervention as soon as abnormalities are noted probably should be included in the care of all patients with asthma. Documentation of levels of fitness may be especially important in patients who require oral corticosteroids because of the known side effects of steroids on muscle strength. While there are no data demonstrating that early initiation of exercise programs in patients with severe asthma can prevent the abnormalities in fitness observed in our patients, it would seem that maintenance of fitness would be easier than rehabilitation once major abnormalities are present.

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Quotables:

Controversial Papers: Those who agree with a controversial paper write to the author; those who disagree write to the editor.

THOMAS MCKEOWN Perspectives in Biology and Medicine 1986

Parent Salvage and Parent Sabotage in the Care of Chronically Ill Children

Penelope Krener, MD, Raymond Adelman, MD

 Adaptive parental behaviors produced from dealing with prolonged illness may sabotage medical care of the chronically ill pediatric patient. Such parental behaviors may be the result of unsuccessful intrapsychic or interpersonal salvage operations in the response to the strains resulting from illness in their child. They may resemble psychopathology, but actually can be reversible. Five cases are presented to illustrate differential diagnosis of parent difficulties ranging from adaptive strain in normal parents to Munchausen's syndrome by proxy in parents of children with chronic illness. A typology of parent-child pathology in health and chronic illness is presented. The literature is reviewed, diagnostic features are elaborated, and management strategies are suggested.

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hildren's responses to severe illness are well described in the literature on the influence of illness on children, the fears they have disclosing pain, and how they signal their caretakers, or avoid disturbing the environment.2-4 Major adaptive tasks described for the child with lifethreatening and terminal illness⁵ are separation, pain, control, and concerns about honesty and trust in communication with medical staff. Given that it is abnormal to be chronically ill,6,7 it is not surprising to find that accommodation to this sad situation produces behaviors that would be labeled deviant for healthy children and their families.

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THE BRUTALIZATION OF CHRONIC ILLNESS

The family of the chronically ill child faces psychological demands to deal with unresolved grief for the child's normalcy or anticipatory grieving for his death. Tactically, the child's illness suspends many family activities, drains financial resources, unbalances the needs of the ill child and those of healthy siblings, and strains the parents' marriage. Medical care and hospitalization typically polarize parental roles. The child's illness skews the balance between dependence and his expected progression toward developing autonomy and control over himself. An experience of diminished parental competence is inevitable. Siblings pay a silent price of helpless anxiety, resentment, and guilt.7

Five ways that the parent must adjust to a child's chronic illness potentially distort so-called good parenting. These are not obligatory features of families with chronically ill children, but they are typical parent maneuvers to salvage their child's development against the corrosion of chronic illness.

First, constant recalibration to the ill child's needs makes it harder for the parent to take readings of his capacities; the ensuing confusion may simulate the "blindness" to developmental capacities for which abusive parents are known. Second, symbiosis or regression of the parent-child pair together, in fact a normal adaptation by the attuned parent to a child's illness, brings with it a certain fusion of feelings of the mother and child, a tilt toward nonverbal communication, and special distancing from persons outside the caring dyad. Third, the ill child's parents commonly doubt their ability to meet all the child's needs. Indeed, nurturing virtuosity is re-

quired to respond to the often contradictory demands of a small person who wants independence but also pampering, and whose "baseline" of capacities is an unstable one. Fourth, if the child is repeatedly hospitalized, and examined and cared for by many physicians and nurses, the parental task of preparing the child to deal with the world becomes impossibly complicated. Indurated by professional encounters, and vigilant for inevitable misunderstandings in the child's care, mothers commonly feel urged to take active roles to spell out their child's needs. and to keep track of medications and treatments. At times, these efforts may resemble authoritarian struggles with staff or overly possessive behavior toward the child. Fifth, for most families, it is operationally socially isolating to have a chronically ill child.

How does the distortion of parenting brought about by chronic illness compare with five typical characteristics of families who actually abuse their children? First, lack of empathy and "blindness" to the child's developmental needs predispose abusive parents to misperceive their children's naughtiness as being bad and punishable. Second, such parents are said to have poor interpersonal boundaries, and in the case of parents with Munchausen's syndrome by proxy, to be characteristically symbiotic with their children. Third, abusive parents have poor nurturing ability, often because they were abused and badly cared for when they themselves were small. Fourth, they exhibit authoritarianism about their children and consider them like possessions, over which they have perfect privileges to deal with in any way they wish, including rights to physically punish them. Fifth, social isolation is commonplace, because the

same interpersonal problems that make it impossible to be a good enough parent also obstruct other relationships.

While "good" adaptation to a chronic illness may be pathological if carried into "normal" settings, nevertheless, it is what the chronically ill child learns as his daily life-style. Parents who acquiesce to the parenting distortions imposed by chronic illness in their child are seen as more tractable and cooperative by health care personnel. Conversely, parents who freely express pain or discouragement over having a suffering child, who admit inconvenience and boredom with care, or impatience with whining and complaints, may be a "management" problem to overtaxed health care service systems that rely on parents for auxilliary support.

Thus similar parenting behaviors may result from several causes. Whether behavior is labeled characterologically dysfunctional or situationally adaptive has to do with its inflexibility to changes in the person's psychosocial environment. However, since the parent of a chronically ill child is more or less trapped in the hospital environment and in the illness context, this is almost an academic concern; the daily business of adjusting to the situation and of communicating with the child's caretakers must go on.

PATIENTS WHO BREAK THE RULES

So-called normal long-term pediatric patients and their parents have these difficulties; however, physical illness also afflicts imperfect persons. Such patients are familiar enough to medicine to have earned their own nicknames: "cranks," "crocks," and "crackpots." They have been more formally termed "difficult," "hateful," or "borderline" patients, 10 who somatize, obfuscate, and complain, but reject help, sabotage remedies, and overuse medical services, or abuse and generally thwart their physicians' best intentions.

For patients with psychosomatic disorders, biologic vulnerability allows their medical illness to flourish in the field of their developmental failures. The illness becomes ingrown to their coping mechanisms and self-image to an extent that blights their medical treatment with complications and relapses. In such families when it is the child who is ill, psychosomatic illness patterns are intimately shared with the parent. 11,12

Factitious illness may evolve from parallel developmental misfortunes; it must be resorted to when the patient's body does not comply with his need to be sick. 13,14 The extreme example of such a patient is the patient with Munchausen's syndrome, 15 and the combination of such pathology with parenthood produces the dramatic form of child abuse termed "Munchausen's syndrome by proxy," a syndrome in which for odd psychological motivations, a parent creates striking and frightening symptoms in their child and tricks physicians into believing that the child is seriously ill, and into making serious diagnostic intrusions. 16-34 Underlying such medical mischief is desperately serious psychopathology, 29,35 with nontrivial symptoms, such as impaired reality testing, alexithymia, somatization, or paranoia, and often maternal histories of significant abuse, and emotional neglect.36,37 Reports of Munchausen's syndrome by proxy that malign parents least are those in which the mother's psychiatric problems are most thoroughly evaluated.29,38

Comparing severely pathogenic parents with Munchausen's syndrome by proxy with parents of chronically ill children reveals superficial similarities. To deceive their child's physicians, parents with Munchausen's syndrome by proxy have taught themselves paramedical skills that parents of chronically ill children cannot avoid acquiring in on-the-job training at the bedside. Medically abusive parents often have histories of abuse, loss, psychiatric or medical problems with many hospitalizations, and marital discord and peripheral spouses. However, her child's chronic illness brutalizes, bereaves, and "hospitalizes" the normal mother along with the child, and dislocates and isolates the family. Psychosomatically pathogenic mothers view the child as valuable, but damaged, and compare his symptoms with their own, but so may any parent when their child is chronically ill. Focusing of maternal attention on the child's body products, blood, urine, and feces, which is taken as a sign of pathology in medically abusive mothers, is an adaptive, almost inevitable behavior of parents at the bedside of their severely sick child. Displays of inseparable maternal devotion, and willingness to relieve staff of care of the child patient, are termed controlling, "limpetlike attachment" in mothers with Munchausen's syndrome by proxy, but such devotion is often seen in any mother of a very sick child, and in short-staffed pediatric wards with "family-centered care," it may be actively encouraged. It is arguable then that chronic illness itself may engender some features of the pathology of Munchausen's syndrome by proxy, particularly when medical noncompliance contaminates the essential partnership among physician, patient, and parent.

The deception of Munchausen's syndrome by proxy is sustained because the parent's behavior may say one thing but their words another. Meadow¹⁸ observes that ironically by doing one's job as a physician, one colludes with the parent's pathogenicity. He declares that diagnostic detection should be made through observing behavioral patterns, since the history is mendacious,18 and he outlines how to do this. Once the diagnosis is made, he finds that confrontation of the parent by the pediatrician works to break the pattern. He emphasizes that psychiatric consultation does not. However, some parents unwittingly sabotage their child's medical care, and while many are "difficult," most are not abusive. They may be troubled or limited, and the sabotage may stem from bungled efforts to salvage some aspect of the child's normal existence or of their own sanity.

Recent increased awareness of the Munchausen's syndrome by proxy and of child abuse in general has led to improved detection, 22.39 and perhaps surprisingly, to overdiagnosis of this unwanted syndrome, even in children with unequivocal chronic illnesses. The Table shows a typology of parent-

| P s v | | | | | |
|---|--|--|---|--|--|
| Parent/Child Behavior | Parent Behavior | Sickness Situation | Yourself Caretaker | C Child Behavior | H Health Care Setting |
| Normal/well | ОК | Usual childhood events | Pediatrician easily treats, no psychiatric needs | Develops well | Routine service use |
| Difficult and disturbed/well | Vexing | Problems, accidents, somatoform disorders | Pediatrician relation strained, may refer to psychiatrist who can help | Behavior problems, psychological illnesses | "Doctor-shoppers" overutilize services |
| Normal/ill (patient 1) | Stressed, but coping | HPI and PMH* coherent | Pediatrician treats; psychiatrist works with team | May be dependent, regressed, or sad | Good alliance with caretakers |
| Difficult/ill (patients 2 and 3) | Hard to communicate medical information | HPI and PMH confusing and complex; many physicians involved | Pediatrician frustrated; psychiatrist often involved and may help | Regressed, uncooperative, or overly limited parental lack of understanding | System perturbed, eg, mobilization of consults, calling many consults |
| Disturbed/ill (patient 4) | May be noncompliant; child may do worse in parents' care | HPI and PMH sounds tragic, with criticisms of previous physicians | Pediatrician thwarted, overwhelmed; psychiatrist hard to give help directly to the patient, except to team | All of above plus behavior problems, symbiosis | Major dislocation of system; maximal administrative impact, or suits |
| Munchausen's syndrome; by proxy/ill (patient 5) | Appear cooperative but harm child by producing signs of serious illness | Elaborate, cunning deceptions, falsifications of records and of body secretions, direct assults on child | Pediatrician is tricked, and is very angry; psychiatric consultation rejected unless court ordered | Child is victim, may collude with parent; usually symbiotic | Excessive utilization deception, becoming adversarial when abuse uncovered |

^{*}HPI indicates history of present illness; PMH, medical history.

child pathology along a continuum, with physically healthy children at one end, and ill victims of Munchausen's syndrome by proxy at the other. At the benign end of the continuum, medical knowledge is required. At the "troubled" end,9 psychological sophistication is demanded to treat the patient's illness without being defeated by psychological problems in the child. the parent, or by emotional responses in yourself, the stressed caretaker. 10,40,41 The physician should locate his patient in this grid. He does this based on systematic assessment of the parent, the sickness situation, including the story of the illness, his awareness of his own responses as a caretaker, his direct observations of the child, and his knowledge of his hospital setting. The acronym "PSYCH" spells in turn the parent, the sickness situation, yourself (the caretaker), the child, and the hospital. Five case vignettes of children with chronic illnesses are alphabetized in order of ascending parental psychopathology and are located in the Table.

ILLUSTRATION OF CASES

Case A.—Juvenile diabetes mellitus was diagnosed at age 5 years in a 14-year-old girl and treated uneventfully until adolescence, when she once experimented with increasing her insulin to lose weight. Diagnosis: V62.89—adolescent life-circumstance problem. Treatment: the pediatrician met with her individually and talked about the difficulties of being different in adolescence. She was then able to understand the anger underlying her dangerous behavior.

Case B .- An 11-year-old boy also had juvenile diabetes mellitus diagnosed at age 5 years. He was considered "brittle" to medical treatment, despite extensive efforts to educate parents, and frequent office visits. His parents failed to ally with the pediatrician or endocrinologist, did not follow advice consistently, and, exhausted. rarely visited him in the hospital during many episodes of ketoacidosis, including one associated with coma and seizures. Psychiatric evaluation disclosed a chaotic family wherein the boy's diabetes had become an entrenched psychosomatic syndrome. Diagnoses: V61.20-parent-child problem, and 313.00-overanxious disorder. Treatment: outpatient psychiatric

treatment over 18 months included behavioral modification until target symptoms resolved, and later play therapy and marital and family therapy was instituted with improved outcome.

Case C .- A 12-year-old girl had liver failure secondary to congenital α_1 -antitrypsin deficiency. Transplantation was delayed by difficulty in finding an organ. Her mother's affective instability was noted during this period and nurses expressed concern about the child's need to be parental to her. The mother did not allow the girl to express anxiety or discomfort. Local television aired the child's vigil for a liver; coincidentally a donor was found through conventional sources. After a successful transplant, the child's mother continued intense encouragment of local media publicity, with frequent televised contact during which she presented herself as saintly and strong. Outwardly cooperative, cool, and in control of her feelings to an extent very unusual for parents whose children are undergoing transplant surgery, the mother was unempathetic as she forced the girl to "buck up and face the cameras."

When the patient went home, the publicity subsided but medical management problems developed. For example, although strictly cautioned against violent

physical activity, mother encouraged the patient to do gymnastics after surgery because it would "make her feel better and help her get her figure back." The patient was readmitted to the hospital with severe organ rejection and undetectable cyclosporine levels, although the dose had been redoubled. The mother protested shocked surprise, yet appeared delighted to be back on the transplant ward. Medical noncompliance was suspected and psychiatric consultation was sought. On interviews, the mother was guarded and maintained a glossy heroic front. Her psychosocial concerns were promptly relayed to the psychiatrist by the nurses, whereupon she denied them, eschewing contact with the consultation liaison team, explaining: "Oh, I just wish they'd leave her alone; they depress her." Diagnosis: the mother, 301.81-narcissitic personality disorder, underlying depression with grandiose experience of having a special child; the patient, 309.00adjustment disorder with depressed mood. Treatment: the patient's mother, with obvious secondary gain from her child's illness, repelled any change in her current adjustment. A strategy was developed to involve the father in regular contact with the care plan, and to encourage the patient in her own self-care. A coordinated treatment approach for the mother's anxiety and impulsiveness helped every encounter with members of her child's care team to be consistent and therapeutic. Outcome: the rejection episode resolved. In this case engaging the healthier parent in monitoring the patient's care, and giving the patient more autonomy, let this preadolescent recover and accomplish age-appropriate developmental separation from her mother.

CASE D.—The condition of a 9-year-old boy with cystinosis deteriorated due to medical noncompliance; he had multiple admissions for dehydration, hypokalemia, and hypophosphatemia, severe weakness, a femoral neck fracture, and other complications. At home, his mother sometimes withheld fluids as a punishment to make him eat. Clinic attendance was erratic despite telephone or written reminders. Herself a survivor of an abusive childhood, the patient's mother was a strong and healthy athlete, with no secondary gain from his illness. In the hospital she was verbally abusive to him. To the psychiatry consultant, in a joint session with the patient, she yelled "how would you feel if you got stuck with a kid like this?" Toward nurses, she was flippant and emotionally uninvested: "Hey I've done my time, riding that windowsill," or acknowledging "Those nurses are OK." She was overtly adversarial to his pediatrician. She devised exploitative re-

lationships with nurses and other parents, receiving loans and meal tickets from them. Although effectively manipulative, she betrayed underlying chaotic neediness and distress and a history suggestive of bipolar mood disorder. We learned that a preexisting pattern of intermittent medical noncompliance had escalated with a family crisis: the murder of the patient's father. The mother's history of carrying out successive liaisons, and various antisocial activity, such as fraud and theft, came to light. She became clinically depressed with vegetative signs after she was jailed for writing bad checks. Diagnosis: the mother, 296.62-mixed bipolar mood disorder, and 301.70-antisocial personality disorder; the patient, 309.00-adjustment disorder with depressed mood. Treatment: intervention was marked by successive failure of behavior modification and family intervention with mother and child. During court-ordered individual psychotherapy, the mother alternated glib recountings of numerous schemes with sad stammerings about obstacles to her happiness. Outcome: protective services removed the patient from the mother's care because of persistent medical noncompliance. In a foster home, there were no further medical management problems. Although the boy thrived medically and resumed growth, he pined for his mother, who, for all her cruel and moody behavior, was still the most dazzling and intimate adult in his life.

Case E .- A 9-year-old girl had nephropathic cystinosis with Fanconi's syndrome complicated by cirrhosis, gastrointestinal tract bleeding, thrombocytopenia, and hemolytic anemia requiring splenectomy. She had multiple hospital admissions for severe electrolyte abnormalities, including marked hyponatremia, hypokalemia, acidosis, and hyperphosphatemia, as well as hypothyroidism, all easily corrected by inhospital administration of the same medications that had been prescribed for her outpatient care. With progression to endstage renal failure, severe hypertension developed, and hyperphosphatemia persisted, resulting in widespread metastatic calcification, involving skin, vasculature, and joints. All four heart valves became calcified, with severe mitral regurgitation and aortic stenosis.

The patient's behavior, clingy, "cute," and regressed, alternated with an "old-beforeher time" worried demeanor. We learned she actively colluded in the medical noncompliance, for example, by stuffing her pills into the sofa upholstery. Her mother had a prior substance abuse disorder, and admitted to drinking binges during the girl's hospitalizations. The patient had once been removed by Children's Protective Ser-

vices because of medical neglect, but was placed with family members and eventually returned home. Protective services told her physician that unless there was active abuse and her life was in "immediate danger" she could not be removed again.

The patient spent hospitalizations quietly in bed with the telephone on her lap, dialing her mother, asking when she would visit, and receiving promises, but frequently her mother did not show up. The mother's behavior toward the girl was irritably fused; she would scold her for being overly demanding and later they would curl up together to sleep or watch television like a pair of kittens. On one hand she complained of the confinement of having an ill, fragile child; on the other she boasted: "Taking care of her is my full-time jobthe only job I can keep!" The child's behavior was fractious, petulant, and mopey when her mother was there, but with other adults, she engaged in a playful curiosity, alleviating her anxious "little-old-lady look. The mother enjoyed the hospital, called staff by their first names, and appeared at the nurses' stations to announce "I'm here now!" A friendly, "regular customer," she felt at home, and for years freely told other parents that her child was dying. Reenacting a familiar adversarial posture toward men, authorities, and physicians through the "uniqueness" of the patient's illness and the need for recurrent admissions, she staged repeated confrontations with the nephrologist. Diagnosis: the mother, 305.92-substance abuse disorder, and 301.50-hystrionic personality disorder: the patient, 309.21-separation anxiety disorder, 315.50-mixed specific developmental disorder, and 309.83-adjustment disorder with withdrawal. Treatment: several treatment interventions failed: hospital consultation resulted in amiable pseudoagreement and no behavioral change. In family sessions, the family appeared guarded and joined ranks with mother, perhaps to preserve their contact with the patient. Calling childrens' protective services did not result in out-of-home placement, and escalated the adversarial process, although subsequently there were fewer missed pediatric renal clinic appointments. However, for court-mandated outpatient psychotherapy there were innumerable missed appointments; the mother claimed she could not get through by telephone but never left messages. When she did come to the psychiatry clinic, she complained that it was boring for the patient. The outcome was progressive deterioration, cardiac calcification, and death. At the girl's funeral, her physicians and nurses were struck by the mother's inappropriate iollity.

COMMENT Hospital Ecology

Chronic illness in children brings about long relationships between children, their parents, and the pediatric caretakers; some of these improve over time while others deteriorate. When relations become strained and fracture with mutual accusations it is not in the sick child's best interest. Responses that are common, even sensible, in healthy settings become disputable in tertiary-care medical settings. For example, it has been estimated that most parents fail somewhat to comply with medical recommendations,6 but in chronic childhood illness, the stakes are higher, the surveillance is better, and this becomes a contended issue.

The etiquette of physician-patient encounters assumes a status gap, with the physician presumed to be more educated and knowledgeable, and imbued with more authority. Accordingly physicians' language, that of medical terminology, prevails. Emotional matters such as patient fears are translated into language of medical symptomatology,6 and comfort giving may take the form of prescriptions. Although we know that "healthy denial" is associated with faster recoveries,5 it implicitly violates communication between the patient and physician. The presence of multiple physicians and nurses fragments clinical observations of the mothers, as well as of the patients. Time-pressured history taking may let certain nonrepresentative actions of stressed parents become metonyms for their whole character, and mistaken details of history, repeated without reexamination, may ossify in the chart. In complex tertiary-care settings with multidisciplinary teams, trainees, and consultants,42,43 communication easily becomes fragmented, caretaker roles may stereotype relationships, and the resulting shallowness of contact fails to correct those distortions. The many medical consultations inflicted on the long-term patient may stimulate growth of parental obsessions on the details of the child's illness, like those spontaneously seen in mothers of Munchausen's syndrome by proxy victims.27 Indeed, possibilities for confusion of patients with victims of Munchausen's syndrome by proxy are proportional to the technological advancement of the medical settings to which they gravitate.⁴²

Chronically ill children inspire side taking. Sincere conflicts of opinion may arise about the child's best interest. Advocacy for the child can at times be opposed to advocacy for the mother or for the harried medical care team. When things go badly enough, the consultation liaison psychiatrist is called in. In the circulation of the hospital, this individual functions somewhat like a mast cell, and goes where there is pain, injury, and inflammation.

However, in the hospital setting, introducing the psychiatrist disequilibrates an already unstable situation. He speaks another "language," that of affects, psychiatric symptoms, developmental increments, defenses, and relationships. This new language must be introduced into an already information-overloaded system. Because the psychiatrist is rarely called during the honeymoon phase of agreement between the parent and physician to comment on how well things are going, he is usually introduced to the parents by the time they are weary of meeting new specialists. They have been socialized to expressing their worries and fears in the language of medical terminology and technological fluctuations. They often deny that their own personal history is important in the matter of their child's care, and as they are trying to keep up their emotional strength, they may not relish having their painful and vulnerable feelings explored. In fact the very summoning of the psychiatric consultant may be seen as a reproach from their pediatrician who might not have had the courage to criticize them to their face.

Management: Optimizing Salvage

In all treatments, to proceed without clear diagnostic definition is reckless. Psychosocial management is no exception. Thus the discussion so far has stressed careful understanding of what goes on behind the symptoms before a plan can be tailored based on a pragmatic assessment of liabilities and resources in the milieu. Progressively intensive strategies are required if the patient is far along the continuum of severity of parental psychopathology.

So-called normal parents of chronically ill children can be assisted in salvaging good developmental experiences with and for their child, by support, honest communication, and shared decision making. The parents of patient 1 (case A) put such support to good use. Parents presenting tough management problems can be helped if their own personal problems can be understood in a nonjudgmental and matter-of-fact way, and if they can be taught to separate their problems from those of their child. Rallying the support of family, clergy, and child psychiatrist can be useful tactics, depending on whom it is easiest for the parent to allow to help them. As in the work with patient 2 (case B), this may be a slow process, passing through several steps of parent growth and moltings of child symptomatology.

If the parent creates tough, variable problems, and if their attempts to salvage their self-esteem take the form of maneuvers that sabotage the treatment, as in case C, it may be necessary to build into the care plan a component of milieu therapy to support the parent enough so that they do not obstruct the child's treatment. In case D, this required considerable staff mobilization, frequent team meetings, putting the psychosocial problem at the top of the problem list, and carrying out careful psychosocial maintenance operations to keep the delicate support structure from fracturing under pressure of fresh crises. Even with this degree of care, medical noncompliance may persist, although not necessarily as in case D, to a degree qualifying for legal removal of the child for medical neglect. Determination of medical neglect is a highly individualized decision heavily influenced by court custom and physician input. If ground is steadily lost in the child's medical care and in the relationship with the family, as in cases D and E, it may be necessary to call a child protective service agency with the goal of offering surveillance with clout. This may provide legal reinforcement for the medical team where persuasion

has failed, or separate the child from the parent if all other measures fail.

Salvage attempts that may be distorted features of "normal" parenting if the child is sick, may become established habits if the child is chronically ill. Strains on parental development are continuous when the child's illness is unremitting, especially if the parent-child pair is removed from the home to the hospital. In some cases the mother sabotages her child's health and his/her medical care in an attempt to salvage her own sanity, to master an earlier impossible challenge, or to live with a personal neurotic conflict. Thus medical noncompliance may occur through neglect, or through active, not always consciously understood, behaviors that are attempts to reenter the medical milieu and freshly master the special challenge created within the parent by the child's illness. Adjustments to abnormal situations may be iterative and insidious; neither the parent nor the physician may preserve enough perspective to accurately detect the skewing in a parent-child relationship that has occurred in the accommodation process. It has been well described that the obstacles to treatment of Munchausen's syndrome by proxy32 stem not only from the disguises that delay recognition but also from the information barrier to the clinical intruder achieved by the symbiosis between mother and child, the convinced and convincing denials of parents, who are in fact unaware of their motives, and the disbelief of legal authorities. However, recognition of subtler parental sabotage is also difficult because of adaptive changes in parenting impelled by the strains of the child's illness.

Why are child psychiatrists so often unable to be useful in these taxing and tragic situations? First, we reemphasize that we deal here with severe psychiatric syndromes. When an illness is grave, one needs not only the right treatment, but enough of it. One psychiatric consultation will not "fix" a deep and malignant developmental problem, even if the psychiatrist knows exactly what the problem is. Treatment of disturbed and characterologically contorted persons is not quick or easy. In reported cases of

treated parents with Munchausen's syndrome by proxy,38,44 treatments were court ordered and long, in terms of years, and used multimodal approaches, such as psychiatric hospitalization for the mother in one case. Bentovim45 states that the child psychiatrist must be integrated within the pediatric hospital, and included in deep involvement with the pediatricians, so assessment of parent and child can be made in a pediatric context. Without regular time and contact, the subtleties of sabotaging conditions such as medical noncompliance and Munchausen's syndrome by proxy will be missed and the liaison psychiatrist will not have a helpful role. No matter how clever he is, if the child psychiatrist cannot combine his observations with those of the medical care team, he is like a tourist trying to achieve the sort of synthesis and analysis worthy of an anthropologist.

Chronic illness defeats the physician, and especially outrages our hopes for our pediatric patients. A stubborn struggle against the child's illness may repeatedly redirect the caring physician toward new medical strategies for its management. In allying with the parents to this end, the medical team may unwittingly collude in the development of abnormal parental behavior. The technological imperative may obstruct secondary prevention by deflecting energy away from psychosocial to medical care. This distracts from experiencing with and enduring with the patient, so the shared victories, when they occur, may be as lacking in humanity as the shared defeats.

CONCLUSION

Chronic illness in children may produce adaptive parental behaviors that resemble psychopathology. Illness also may occur in families where psychopathology preexists and at times it potentiates such psychophathology. Parental behaviors that sabotage medical care of their children may be the result of unsuccessful intrapsychic or interpersonal salvage operations. It is important to distinguish these from more malignant behaviors that sabotage the child's medical treatment because of conscious or unconscious pa-

rental inner conflicts about the ill child. A typology of parent-child pathology in health and chronic illness has been presented, ranging from adaptive strain in normal parents to Munchausen's syndrome by proxy in parents of children with chronic illness. Diagnostic features have been elaborated and illustrated with case histories, and management strategies suggested.

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In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY-HEAD & NECK SURGERY Histopathologic Review of Salivary Gland Tumors in Childhood

Ernest E. Lack, MD, Melissa P. Upton, MD (Arch Otolaryngol Head Neck Surg 1988; 114:989-906)

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No evidence of impoired fertility was shown in laboratory animal reproduc-

Hon studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cramolyn special common studies with cramolyn special common studies with cramolyn special common studies are studied in common studies. The studies with the studies of sections of sees produced no evidence of fetal malformations. Adverse fetal malformations. Adverse fetal of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced malfernal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

ing pregnancy only it clearly needed.

Drug Interaction During Pregnancy:
Cromolyn sodium and isoproterenol
were studied following subcutaneous
injections in pregnant mice. Cromolyn
sodium alone in doses of 60 to 540
mg/kg (38 to 338 times the human
dose) did not cause significant increases in resorptions or major maltordose) aid not cause significant in-creases in resorptions or major matior-mations, isoproterend alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and matiormations. The addition of cromo-tifyin sodium (338 times the human dose) to isoproterend (90 times the busine dose) annexes to huma inhuman dose) appears to have in-creased the incidence of both resorp-tions and malformations.

Mursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NA-SALCROM is administered to a nursing woman

Pediatric Use: Safety and effective-ness in children below the age of 6 years have not been established.

years have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions accurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nosal strigling (1 in 20), nosal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad laste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients. One patient in the clinical trials developed anaphyloxis.

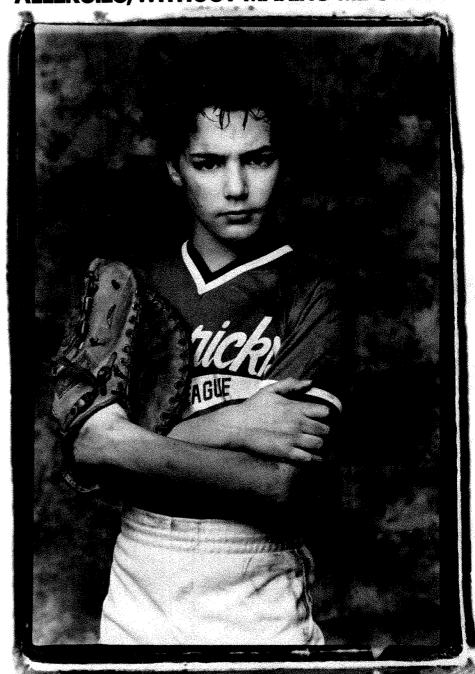
trials developed anaphylaxis.

Adverse reactions which have oc-curred in the use of other cromolyn sodium formulations for inhalation in sodium formulations for inhalation in-clude angioedema, joint pain and swelling, urticaria, cough, and wheez-ing. Other reactions reported areity are serum sickness, periarteritic vascu-litis, polymyositis, pericarditis, photo-dermatitis, exfoliative dermatitis, pe-ripheral neuritis, and nephtosis.

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Data on file, Fisons Corporation, From perennial allergic rhinitis trial by Wiftig HJ, with Cohan RH, Bloom FL, Rhoades RB, et al.

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Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio Fredric Burg, MD, Philadelphia Harold Levine, MPA, Galveston, Tex Barbara Starfield, MD, Baltimore Larrie W. Greenberg, MD, Washington, DC



Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—This article discusses a new and important concept in pediatric cardiology. Preventive cardiology clinics seem to be springing up all over the country. How many clinics and what services are available to our patients? What is required to start such a clinic? This survey addresses these questions.—H.D.A.

Pediatric Preventive Cardiology Clinics

J. Timothy Bricker, MD; Richard M. Schieken, MD; William B. Strong, MD

Atherosclerotic cardiovascular disease is the leading cause of death in the adult population in our society. Cardiac diseases due to diphtheria, rubella, and rheumatic fever are currently extremely rare in comparison with the incidence in previous generations.1 This is, to a great extent, due to successful practice of preventive medicine in the offices of pediatricians. Although the clinical manifestations of atherosclerotic cardiovascular disease seem to be in the distant future for children, there is good evidence that the pathological process begins in childhood. 1-6 Furthermore, there is no question that behavioral aspects of a coronary disease-prone life-style have their roots in childhood. 5.7 Efforts directed at the prevention of adult atherosclerotic cardiovascular disease are being increasingly incorporated into

the practice of pediatrics.

Pediatric preventive cardiology clinics have developed in the recent past for several reasons. The incorporation of preventive cardiology efforts in pediatric practice leads to the identification of patients who the pediatrician wants evaluated further or treated in a tertiary center. These patients potentially benefit from the presence of an organized pediatric preventive cardiology clinic at the medical center. The multidisciplinary nature of a preventive cardiology clinic leads to coordination of services available to the patient. In some instances, pediatric preventive cardiology clinics have been developed for house staff and medical student education. Preventive cardiology clinics in pediatric departments also have been developed for purposes of clinical research.

REASON FOR THIS SURVEY

At a recent conference regarding preventive cardiology practice, the question of the number and scope of pediatric preventive cardiology clinics was raised. We were aware of several such clinics but had no specific information in this regard. A ques-

tionnaire was developed for the following purposes: (1) to become aware of clinicians who may be proceeding in a different, and perhaps better, manner than we are in our own pediatric preventive cardiology clinics; (2) to develop a list of active or beginning clinics that might be willing to participate in clinical trials of new therapies that would not be possible at any one center; (3) to develop a list of clinicians interested in this field for use when patients move to other parts of the country or when pediatricians call from other areas of the country with questions about a specific patient; (4) to assess the availability of clinic directors potentially interested in the setting and reviewing of guidelines; (5) to obtain an address list for the possible future dissemination of information regarding educational materials or the availability of funding in this field by the National Institutes of Health, Bethesda, Md, and others; and (6) to evaluate trends in costs and reimbursement in pediatric preventive cardiology.

DISTRIBUTION OF THE QUESTIONNAIRE

A one-page questionnaire was distributed to pediatric department chairpersons (listed by the Association of Medical School Department Chairmen), pediatric cardiol-

Reprint requests to Pediatric Cardiology, Texas Children's Hospital, 6621 Fannin, Houston, TX 77030 (Dr Bricker).

Accepted for publication April 18, 1988.
From the Baylor College of Medicine, Houston (Dr Bricker); the Medical College of Virginia, Richmond (Dr Schieken); and the Medical College of Georgia, Augusta (Dr Strong).

Table 1.—List of 25 Currently Functioning Pediatric Preventive Cardiology Clinics and 20 That Are Scheduled to Open in 1988

| Institution | Person to Contact |
|--|-----------------------------|
| California | I Kochani |
| University of California, San Diego University of Southern California | I. Kashani A. Hohn |
| University of Southern California Colorado | |
| University of Colorado | R. Wolfe |
| District of Columbia | |
| National Children's Medical Center | K. Kuehl |
| Uniformed Services University for Health Sciences | J. Moore |
| Seorgia | W. Strong |
| University of Georgia | T. Subjug |
| Rush-Presbyterian-St Luke's Hospital | H. Bucheleres |
| University of Chicago | D. Ruschhaupt |
| ouisiana | |
| Tulane University | A. Pickoff |
| Massachusetts | J. Newberger |
| Harvard Medical School | J. Newberger |
| Michigan Michigan State University | A. Sparrow |
| University of Michigan | A. Rocchini |
| Wayne State University | W. Pinsky |
| Minnesofa | |
| Mayo Medical School | W. Weidman |
| Missouri | A. Strauss |
| Washington University St Louis University | S. Nouri |
| St Louis Offiversity Nebraska | G11105 |
| University of Nebraska | P. Hofshire |
| New Hampshire | |
| Dartmouth Medical School | S. Rockenmacher |
| New York | |
| Albert Einstein University | C. Steeg |
| Columbia University | W. Gersony K. Hirschhorn |
| Mount Sinai New York Medical College | C. Williams |
| Schneider Children's Hospital | N. Grootman, M. Jacobson |
| SUNY Health Science Center | M. Schiller |
| Newfoundland | <u></u> . |
| Memorial University of Newfoundland | A. Davis |
| North Carolina | T. Boat |
| University of North Carolina, Chapel Hill | I. Boar |
| Ohio Case Western Reserve University | M. Jacobstein |
| Ohio State University | D. Teske |
| Toledo University | J. Hennessy |
| University of Cincinnati | D. Schwartz |
| Oklahoma | P. Blacklett |
| University of Oklahoma | r. Diackiett |
| Ontario Hospital for Sick Children Toronto | V. Rose |
| Hospital for Sick Children, Toronto McMaster University | W. Conner |
| Pennsylvania | |
| Temple University | R. Donner |
| University of Pennsylvania | H. Wagner, J. Cortner |
| Quebec | C Blaichman |
| Montreal Children's Hospital | S. Blaichman |
| Tennessee | T. DiSessa, B. Alpert |
| University of Tennessee, Memphis Vanderbilt University | T. Graham |
| Vanderbilit University Texas | |
| Baylor College of Medicine | T. Bricker, W. Klish |
| University of Texas, Southwestern Medical School | D. Fixler |
| Vermont | D. O. HW |
| University of Vermont | R. Colletti |
| Virginia | R. Schieken |
| Medical College of Virginia | H. Schieken M. Gutgesell |
| University of Virginia | III. Galgeoon |
| West Virginia University of West Virginia, Huntington | C. Gushurst |
| Wisconsin | |
| | S. Rao |
| University of Wisconsin | D. Nudel |

ogy program directors,8 and National Institutes of Health preventive cardiology academic awardees in an attempt to identify individuals in their institutions with an interest in this area. A brief cover letter reviewed the purposes of the questionnaire, as discussed above.

RESULTS

We obtained 52 responses to the questionnaire. Twenty-five centers indicated that a pediatric preventive cardiology clinic was already functioning as of December 1987, and 20 centers communicated plans for beginning a pediatric preventive cardiology clinic in 1988 (Table 1). In many circumstances, institutions with no plans to initiate a pediatric preventive cardiology clinic had similar alternative clinics in effect. For example, children with hyperlipidemia at Cornell University Medical Center, New York, are followed up in collaboration with the Rockefeller University Lipid Research Project and in a separate clinic if they are hypertensive. In other institutions, such as the University of Minnesota, Minneapolis, children are followed up in the preventive cardiology program of the Department of Internal Medicine. Several responses indicated that these patients would be evaluated in the general pediatric clinics, the general pediatric cardiology clinic, or by private practice pediatricians without other referrals.

Each of the 25 pediatric preventive cardiology clinics already in operation offered evaluation and management of hyperlipidemia. Nutritional evaluation and therapy was also part of each of these clinics. Evaluation and management of hypertension was included at 14 of these clinics. Eleven of 25 pediatric preventive cardiology clinics included smoking prevention and cessation among the services offered. Management of adult family members is performed at nine of these clinics, either in conjunction with an internist participating in the clinic or limited management with a referral of the more severe adult cases (Table 2).

Current staffing at these clinics included a pediatric cardiologist and a dietician in almost all instances (Table 3). Less than half of these clinics had pediatric house staff or medical student involvement as yet. Inclusion of

Table 2.—Services Provided in 25 Pediatric Preventive Cardiology Clinics

| Service Provided | No. of Clinics |
|-------------------------------|-------------------|
| Nutritional evaluation and | |
| management | 25 |
| Hyperlipidemia evaluation and | |
| management | 25 |
| Exercise testing and | |
| recommendations | 18 |
| Referral of adult family | |
| members | 15 |
| Hypertension evaluation and | |
| management | 14 |
| Smoking prevention and | |
| cessation | 11 |
| Management of adult family | |
| members | 9 |
| Stress management | 3 |

| Table 3.—Current Staffing Strategi | |
|--|----|
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| in 25 Pediatric Preventive Cardiological | |
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| | |
| Clinics | |

| Staff Members | No. of Clinics | |
|---------------------------------|-------------------|--|
| Pediatric cardiologist | 18 | |
| Dietitian | 18 | |
| Nurse | 15 | |
| Psychologist | 9 | |
| Exercise physiologist | 9 | |
| Medical students | 7 | |
| Adult cardiologist | 7 | |
| Pediatric house staff | 7 | |
| Ambulatory service pediatrician | 7 | |
| Post-residency fellows | • | |
| Adult cardiology | 2 | |
| Pediatric cardiology | 2 2 | |
| Pediatric gastroenterology | 1 | |
| Preventive cardiology | 1 | |
| Social service | 4 | |
| Pediatric gastroenterologist/ | | |
| nutritionist | 3 | |
| Epidemiologist | 2 | |
| Patient education specialist | 2 | |
| Pediatric endocrinologist | 2 | |
| Geneticist | 2 | |
| Adolescent medicine specialist | 2 | |
| Pediatric nephrologist | 1 | |
| Smoking cessation expert | 1 | |

psychologists, exercise physiologists, ambulatory service pediatricians, adult cardiologists, epidemiologists, pediatric gastroenterologists, pediatric nephrologists, pediatric endocrinologists, adolescent medicine service pediatricians, social workers, patient educators, and smoking cessation experts on the staff of pediatric preventive cardiology clinics around the country reflects the multidisciplinary nature of attempts to prevent atherosclerotic cardiovascular disease, with emphasis varying from clinic to clinic.

The number of patients evaluated to date ranged from eight to 300 in individual clinics, with a mean of 86 patients. Many clinics were very recently begun, and only 13 clinics had evaluated 50 or more patients. Great variability was found in the follow-up frequency, ranging from monthly to yearly, with more frequent visits typically planned shortly after the initial evaluation. There were 240 children followed up who were found to have cholesterol levels over 7.11 mmol/L (275 mg/dL) at these centers. Of these, 190 (79%) are being treated pharmacologically for hypercholesterolemia. Cost for initial evaluation was in the \$150 to \$200 range at most centers. Initial evaluation was free at one research clinic and was \$30 at two others. The cost of laboratory evaluation was an additional \$30 to \$150 in most centers. Costs of the evaluation in Canadian programs were considerably lower than at the centers in the United States.

COMMENT

Many of the pediatric preventive cardiology clinics have been recent additions to medical school pediatric departments in the United States and Canada. A number more are planned in response to obvious needs for patient care, education of medical students and residents, and clinical research. Although these clinics will serve a useful function, it is only feasible and desirable for the small proportion of the patients who are at the highest apparent risk to be followed up in this type of a clinic. In fact, the majority of pediatric preventive cardiology practice will, of necessity, occur in general pediatric practice. Pediatric training programs will need to develop mechanisms for preparing pediatricians in the practice of pediatric preventive cardiology. A rational strategy for pediatricians to reduce risk in all children, not just those at very high apparent risk, is required. 9-11 Educational materials and techniques developed at these pediatric preventive cardiology clinics will be useful to pediatricians in this regard. These clinics may serve as a source of patients for collaborative multi-institutional trials.

The family at increased risk for future coronary disease includes those with (1) a family member who suffered a myocardial infarction before age 55 years; (2) family members with levels of low-density lipoprotein cholesterol exceeding the 75th percentile for age: (3) family members with excessively low levels of high-density lipoprotein cholesterol in the family; (4) a family history of hypertension and/or stroke; (5) a family tendency for excessive weight gain at any age, especially excessive weight gain during adulthood; and (6) a smoker in the household.12 Children in these families are particularly in need of effort to prevent future coronary disease. The ideal preventive program will be a cost-effective, time-efficient set of interventions that can be initiated and monitored by the child's pediatrician.

That there is great variability in services offered and in staff involved in the pediatric preventive cardiology clinics represented in this survey is neither surprising nor bad. Many of these clinics are in early phases of development, and there is room for flexibility in developing an optimal approach to this group of patients. The majority of clinics seem to be appropriately involved in lipid level-lowering efforts. We would exhort experts at these clinics to adopt broader objectives in the prevention of cardiovascular disease. Development of services for smoking prevention and cessation should certainly be considered at clinics at which this is not offered currently. One of the greatest opportunities that these clinics present is the possibility of training pediatric residents in the practice of preventive cardiology. Pediatric preventive cardiology clinics can be used to a greater extent in the education of medical students and residents than our survey indicates is currently the case. Input from specialists, such as adolescent medicine pediatricians, who have only been considered at a few clinics, could eventually be found to be of great importance in the practice of pediatric preventive cardiology in the future. Efforts to keep costs of pediatric preventive cardiology clinic evaluation as low as possible are necessary. We hope that information from this survey

might be of use to those who are developing or planning pediatric preventive cardiology clinics. Undoubtedly, for a variety of reasons, it is very likely that a number of pediatric referral centers with interests in pediatric preventive cardiology were not represented in this survey. We would appreciate being alerted to other efforts in pediatric preventive cardiology clinics that were excluded from this survey.

This study was supported by grant 1K07HL01940-01 from the National Heart, Lung, and Blood Institute, Bethesda, Md, Preventive Cardiology Academic Award.

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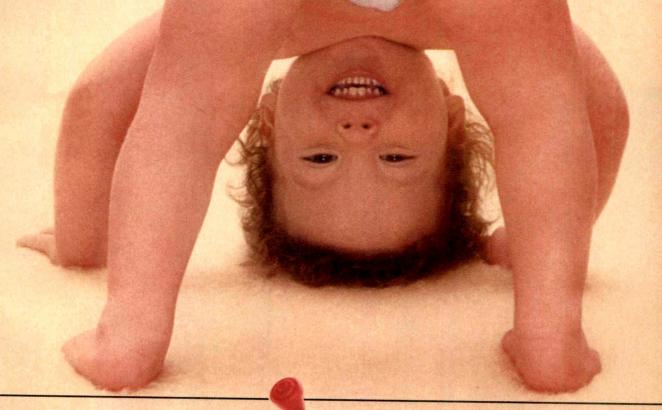
ARCHIVES OF NEUROLOGY

Childhood Adrenoleukodystrophy: Failure of Intensive Immunosuppression to Arrest Neurologic Progression

Sakkubai Naidu, MB, BS; Michael J. Bresman, MD; Diane Griffin, MD; Susan O'Toole, RN, MS; Hugo W. Moser, MD (Arch Neurol 1988;45:846-848)



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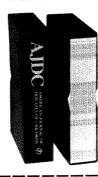
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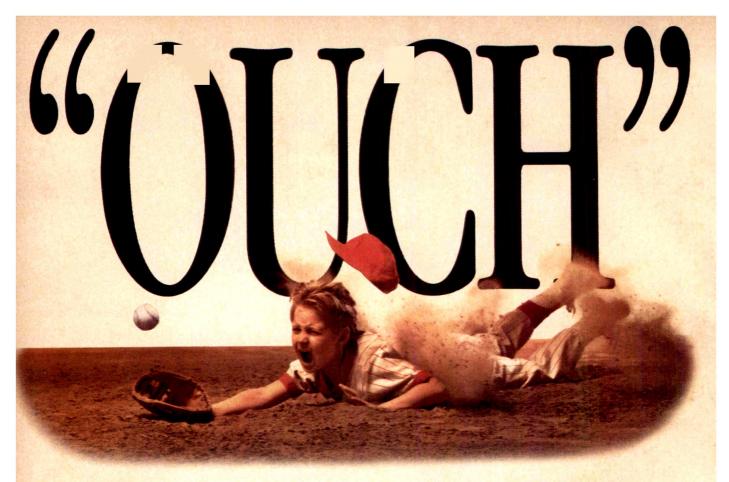
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Laboratory and Clinical Variables to Predict Outcome in Hemolytic-Uremic Syndrome

Peter L. Havens, MD, MS; P. Pearl O'Rourke, MD; Jin Hahn, MD; Joseph Higgins, MD; Alexander M. Walker, MD, DrPH

 To develop a guide to the prognosis of children with hemolytic-uremic syndrome, we reviewed the medical records of 78 patients with this diagnosis seen at The Children's Hospital, Boston, from 1976 through 1986. Two outcome groups were defined as follows: a "good outcome" group, which contained 6 patients with no serious sequelae at hospital discharge, and a "bad outcome" group, which contained 12 patients who died, had chronic renal failure, or had central nervous system sequelae at hospital discharge. Differences between the two groups in routine laboratory tests available within 48 hours of admission were identified by bivariate analysis. Using serum calcium (≤2 mmol/L) plus urine output (<0.4 mL/kg/h) over a 24hour period as a test to predict outcome, we identified patients who died, had chronic renal failure, or had serious central nervous system sequelae, with 75% sensitivity, 98% specificity, and 90% positive predictive value.

(AJDC 1988;142:961-964)

Hemolytic-uremic syndrome (HUS) is defined by the presence of microangiopathic hemolytic anemia, thrombocytopenia. and azotemia. Most often occurring with a diarrheal prodrome in children younger than 5 years old, the syndrome has been reported in persons of all ages and in association with many different illnesses, organisms, and medications. Since the mid-1970s, the accepted treatment for children with HUS has been supportive care alone, and with improvements in dialysis and general patient care, the mortality rate has decreased from about 21% before 19741 to 4% to 7% by the mid-1980s.24 In addition to this mortality, significant morbidity occurs in 10% to 20% of patients who are left with chronic renal failure (CRF), hypertension, or severe neurologic sequelae. Less common complications include colitis with perforation, intussusception, rhabdomyolysis, diabetes or pancreatic necrosis, and myocardial dysfunction.

Various therapies have been tried to

improve the outcome of patients with HUS, but because of the variability of the underlying disease, the strong secular trend toward better outcome from improvements in supportive care alone, and the small numbers reported, it is impossible to say that any therapy is truly useful. Trials of new therapies require early identification of patients with comparable clinical characteristics who are at high risk of a bad outcome. This study was undertaken to develop a test that could identify patients with HUS at high risk of death, CRF, or serious neurologic sequelae based solely on laboratory tests or easily measurable clinical signs available within the first 48 hours of hospitalization.

MATERIALS AND METHODS

Medical records were reviewed of children seen at The Children's Hospital, Boston (CHB), between 1976 and 1986 with a discharge diagnosis of HUS. This corresponded to *International Classification of Diseases (ICD)* code 792(c) from 1976 to 1978, *ICD* 283.9 in 1979, and *ICD* 283.1 since 1980. Of 103 medical records chosen for review, four were unobtainable, 19 had been miscoded and were excluded as not HUS, one was excluded because the diagnosis was made before the study period, and one was excluded for lack of follow-up information. This left 78 patients for study.

Medical records were abstracted by three of us (P.L.H., J.H., and J.H.) using a standard data collection form. Information was collected on history, hospital phase of illness, and outcome at hospital discharge. The laboratory values abstracted were complete blood cell count and differential cell count with reticulocyte count, prothrombin time, partial thromboplastin time, fibrinogen, sodium, potassium, bicar-

bonate, serum urea nitrogen, creatinine, calcium (Ca), glucose, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, amylase, and urine output. These values were recorded for the following time points: first hospital admission (if other than CHB), admission at CHB, first and second 24 hours of stay at CHB, and discharge.

For each of the laboratory variables abstracted, we identified the maximum or minimum value in the first 48 hours of hospitalization at CHB. The urine volume for each 24-hour period was recorded, calculated as milliliters per kilogram per hour, and the minimum value was identified for each patient.

Outcome was categorized by condition at hospital discharge. Group 1, the "good outcome" group, included patients with no serious sequelae at discharge. Patients needing dialysis in the hospital only and those with other in-hospital complications that did not result in death or disability after discharge from the hospital were included in group 1 (Table 1). Group 2, the "bad outcome" group, included children who when discharged from the hospital had focal or global neurologic deficits, needed long-term dialysis, or had hypertension requiring drug therapy. Those patients who died were also in group 2 (Table 1).

For all the variables collected, the mean values in group 1 and group 2 patients were compared, and the Wilcoxon rank-sum test was used to assess the statistical significance of the differences. Fisher's exact test was used to evaluate the statistical significance of the relationship of the categorical variables to outcome. Because of the large number of comparisons made, the cutoff for statistical significance was chosen to be $P \leq .01$. Sensitivity, specificity, and positive predictive value were then calculated for all the variables that differed significantly between the two groups and for all pairs of these variables to identify the variable or combination of variables that would best predict outcome. Data were analyzed using SAS-PC version 6.02.

RESULTS

The yearly variation in the number of cases is shown in Fig 1; there seems to have been an epidemic in 1985, when there were more than twice the aver-

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| | | Systems In | volved | |
|----------------|--|-----------------------------------|------------------------|------------------------------|
| Patient No. | Gastrointestinal | Neurologic | Other | |
| | | Group 1 Patients | ,* | |
| 13 | TO TO THE PROPERTY OF THE PROP | Seizure | • • • | • • • |
| 14 | • • • | Seizure | | Respiratory arrest |
| 15 | ••• | | Hypertensive crisis | Respiratory arrest |
| 16 | ••• | Cerebral edema and stupor | | ••• |
| 30 | | Hallucinations | ••• | Pleural effusion |
| 38 | ••• | Transient hypotonia | • • • | ••• |
| 63 | Colonoscopy (colitis) | | ••• | Ventricular arrhythmias |
| 64 | Intussusception and appendectomy | | • • • | |
| | | Group 2 Patients | ut . | |
| 3 | Rectal prolapse and hemorrhage | Middle cerebral artery infarct | • • • | Death |
| 4 | Colectomy | Focal encephalopathy | | Diabetes and pulmonary edema |
| 6 | Laparotomy (no perforation) | Basal ganglion infarction | ••• | • • • |
| 7 | *** | Multiple infarcts | • • • | Myocardial infarction |
| 11 | Colectomy | Coma and global deficit | ••• | ••• |
| 12 | | Basal ganglion infarction | | Death |
| 17 | Colectomy | Right hemiparesis | Renal failure | |
| 18 | • • • | | Chronic hypertension | Pulmonary edema |
| 19 | | Occipital infarction | ••• | Death |
| 20 | | Coma and focal seizures | ••• | Death |
| 23 | • • • | Seizures and multiple infarctions | *** | Death |
| 24 | | Coma and multiple seizures | • • • | Deep venous thrombosis |

^{*}Patients with a good outcome (complicated hospital course but no sequelae at hospital discharge). †Patients with a bad outcome (death or permanent disability at hospital discharge).

age number of cases. Monthly variation shows an increase of cases in the summer months (Fig 2). There was no association of outcome and time of year that the disease was diagnosed. Age at hospitalization varied from 6 months to 16.5 years, with a mean \pm SD of 4.8 ± 3.7 years and a median of 3.6 years (2.2 and 6 years; 25% and 75% quartiles, respectively).

There were 78 patients with HUS studied—44 males and 34 females. In 24 cases, there was another family member who had diarrhea. One family had two members with HUS, both of whom did well. Twelve patients were

in group 2: of these patients, five died and seven had serious sequelae at discharge (Table 1). Sixty-six patients were in group 1; eight of these patients had a complicated hospital stay but no serious problems when discharged (Table 1), and 58 patients had an uncomplicated hospital course and no sequelae when discharged.

Table 2 shows the relationship of selected clinical variables and outcome. All 78 patients had a diarrheal prodrome that lasted an average of eight days. Duration of diarrhea or presence of bloody diarrhea were not associated with outcome. Neurologic

symptoms were present in the prodromal phase in 29% (19/66) of group 1 patients and 75% (9/12) of group 2 patients ($P \le .006$). Neurologic signs (seizures, coma, focal neurologic deficits, and alterations in mental status requiring endotracheal intubation) were present more frequently in the bad outcome group (P<.0001). Dialysis was done in a higher percentage of group 2 patients than group 1 patients, but 33% (22/66) of the group 1 patients needed dialysis. The mean duration of dialysis was longer in the group 2 patients (13 days) than in the group 1 patients (six days) (P = .04). On average, group 2 patients were 1.6 years older than group 1 patients (P=.4). Group 2 was 75% male (9/12), and group 1 was 53% male (35/66) (P = .21).

Table 3 shows the maximum and minimum values from the first 48 hours of hospitalization for selected laboratory variables and their association with outcome. Group 2 patients had a higher mean percentage of bands; higher mean levels of potassium, creatinine, and glucose; and lower mean levels of serum calcium than group 1 patients ($P \le .01$). There was no statistically significant difference (P>.01) between the two groups in mean values of total leukocyte count, mean hematocrit, reticulocytes, platelets, prothrombin time, partial thromboplastin time, bicarbonate, serum urea nitrogen, creatine kinase, lactic dehydrogenase, or amylase. Laboratory data obtained at admission to other hospitals (before transfer to CHB) were not associated with an outcome group, but many of those data were incomplete in our records. The mean maximum systolic or diastolic blood pressure did not differ greatly between group 1 (113/76 mm Hg) and group 2 (120/79 mm Hg).

Table 3 also shows the minimum mean daily urine volume for the first two days in the hospital. Minimum mean daily urine output in the group 2 patients was 72% of that in the group 1 patients (P = .0009).

We used the results of this analysis of the data obtained within the first 48 hours of hospitalization to develop a criterion to predict inclusion in the bad outcome group. While five of the

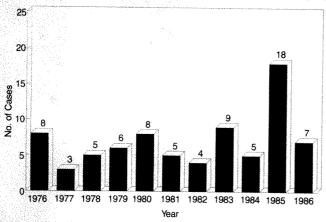


Fig 1.—Number of hemolytic-uremic syndrome cases by year of incidence.

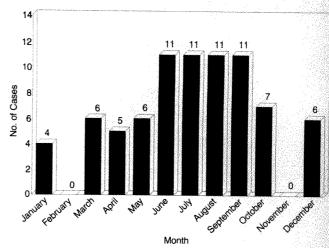


Fig 2.—Number of hemolytic-uremic syndrome cases by month of

laboratory tests had mean values that were significantly different (statistically) between the two groups, most of these were not useful as predictors of outcome because of overlap. The variables that best discriminated between good and bad outcome groups were the serum potassium and Ca levels and the hourly urine output over the first 48 hours. Table 4 shows the sensitivity, specificity, and positive predictive value for each of these variables alone and in combinations of laboratory values with the urine output. The positive predictive value was maximized when the test used was the minimum urine output plus the minimum serum Ca level (Tables 4 and 5). When a positive test was defined as a Ca level of 2 mmol/L or less and urine output of less than 0.4 mL/kg/h (over a 24-hour period), the sensitivity was 75%, the specificity was 98%, and the predictive value of a positive test was 90%. That is, of ten persons who met those criteria at 48 hours of hospitalization, nine had a bad outcome (Table 5). No other variable or combination of variables resulted in equal sensitivity, specificity, or positive predictive value.

The bad outcome definition did not include persons who had a complicated hospital course but no serious sequelae at hospital discharge (listed in Table 1). If the bad outcome definition were expanded to include the eight patients in Table 1 who were all well at hospital discharge despite a complicated hospital stay, giving a total of 20

| Clinical Factors | Group 1, Good Outcome* (n = 66) | Group 2, Bad Outcome* (n = 12) | PH |
|-----------------------------|---------------------------------------|--------------------------------------|----------------|
| Bloody diarrhea | 51 | 10 | Not significan |
| Veurologic symptoms | 19 | 9 | .006 |
| One seizure | 3 | 8 | < .0001 |
| ocal seizures | 1 | 5 | <.0001 |
| fore than one seizure | 0 | 7 | <.0001 |
| Coma | 2 | 10 | <.0001 |
| ocal neurologic examination | 1 | 8 | <.0001 |
| ntubation | 2 | 9 | <.0001 |
| n-hospital dialysis | 22 | 11 | < 0001 |

Age, y

Urine output, mL/kg/h

[†]One-sided P values calculated using Fisher's exact test.

| Variable | Total (n = 78) | Group 1 (n = 66) | Group 2 (n = 12) | Pt |
|---------------------------------------|-----------------------------------|---------------------|---------------------|--------|
| Hematologic variables | 1000 | | | |
| White blood cells × 1000 (max) | 18.5 ± 8.5 | 17.2 ± 6.3 | 26.3 ± 14.3 | .04 |
| Bands, % (max) | 15 ± 11 | 13±10 | 23 ± 11 | .01 |
| Hematocrit (min) | $\textbf{0.22} \pm .06$ | 0.21 ± 0.06 | 0.24 ± 0.06 | .05 |
| Reticulocytes (max) | $\textbf{0.08} \pm \textbf{0.06}$ | 0.08 ± 0.06 | 0.04 ± 0.02 | .06 |
| Prothrombin time, s (max) | 13.2 ± 2.2 | 12.9 ± 1.7 | 14.9 ± 3.4 | .03 |
| Serum chemistry values | | | | |
| Sodium, mmol/L (min) | 131 ± 5 | 132±5 | 127±5 | .02 |
| Potassium, mmol/L (max) | 4.8 ± 0.8 | 4.7 ± 0.6 | 5.6 ± 1.2 | .002 |
| Glucose, mmol/L (max) | 7.3 ± 4.6 | 6.6 ± 2.1 | 11.4±9.8 | .01 |
| Calcium, mmol/L (min) | 2.1 ± 0.2 | 2.1 ± 0.2 | 1.8 ± 0.1 | <.0001 |
| Creatinine, µmol/L (max) | 336 ± 248 | 309 ± 248 | 504 ± 168 | .007 |
| Aspartate aminotransferase, U/L (max) | 87 ± 102 | 69 ± 39 | 189 ± 224 | .04 |

 4.8 ± 3.7

 0.92 ± 1.07

Table 3.—Laboratory Values Within the First 48 Hours of Hospitalization and Their

 4.5 ± 3.4

 0.96 ± 0.83

 6.1 ± 5.0

 0.69 ± 2.02

0009

^{*}See Table 1 for definitions

^{*}Values are given in mean ± SD. Max indicates maximum; min, minimum. †Computed using Wilcoxon's rank-sum test.

Table 4.—Laboratory and Clinical Variables as Predictors of Outcome in Hemolytic-Uremic Syndrome

| | | | Positive Predictive |
|----------------------------|----------------|----------------|------------------------|
| Test | Sensitivity | Specificity | Value |
| Potassium, ≥5.5 mmol/L | .58(.31, .81)* | .93(.85, .98) | .64(.35, .85) |
| Creatinine, ≥2.7 μmol/L | .83(.55, .95) | .56(.44, .67) | .25(.15, .41) |
| Calcium, ≤2 mmol/L | .75(.47, .91) | .74(.63, .83) | .34(.19, .54) |
| Urine output, <0.4 mL/kg/h | .91(.65, .99) | .75(.64, .84) | .40(.25, .59) |
| Potassium per UOP† | .58(.32, .81) | .98(.92, 1.00) | .87(.53, .98) |
| Creatinine per UOP† | .83(.55, .95) | .80(.69, .88) | .43(.26, .63) |
| Calcium per UOP† | .75(.47, .91) | .98(.92, 1.00) | .90(.60, .98) |

^{*95%} confidence limits.

children with bad outcomes, the sensitivity of the combination of Ca levels of 2 mmol/L or less and urine output of less than 0.4 mL/kg/h as a predictive criterion would be reduced to 50%. However, the specificity and positive predictive value would both increase to 100%. Therefore, this loosening of the definition of outcome group does not significantly alter the results of the initial analysis in which the outcome groups were demarcated by clearly defined clinical criteria at hospital discharge.

COMMENT

We have developed a simple prognostic guide based on objective criteria available within 48 hours of hospitalization to identify patients with HUS who are at high risk of death, CRF, or serious neurologic sequelae. In our population of 78 patients with HUS, there were 12 (15%) who fit into this bad outcome group. The use of Ca levels of 2 mmol/L or less and urine output of less than 0.4 mL/kg/h as a prognostic guide predicts patients with bad outcome with 75% sensitivity, 98% specificity, and positive predictive value of 90% (Table 5).

Predictive value varies as a function of the prevalence of the condition tested. While we have found a test that has a positive predictive value of 90% in a population with a prevalence of bad outcome of 15%, the predictive value would drop to 85% in a population with a prevalence of bad outcome equal to 10%, even though the sensitivity and specificity remain unchanged.

In a study of heparin therapy in HUS, Vitacco et al⁵ identified, within

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a "few hours of admission," a high-risk group of 30 patients in a population of 178 total patients based on the presence of any one of the following: anuria, multiple seizures or coma, profuse gastrointestinal bleeding, retinal hemorrhage, a serum potassium level greater than 7.5 mmol/L, a bicarbonate level less than 8 mmol/L, or a diastolic blood pressure greater than 90 mm Hg. The high-risk group identified in this way had a 30% mortality, compared with 7% overall; other sequelae were not reported. The Ca and urine output criteria used in our study distinguish two groups from a starting population of 78 patients—a group of 68 patients with 4% risk of death or serious sequelae and a group of ten patients with a 90% probability of death or serious sequelae.

Similar associations of outcome and serum Ca levels have been found in other studies of HUS. Bale et al,6 in a study of 60 patients, found lower sodium and Ca levels and higher glucose and creatinine levels in their patients with neurologic signs and symptoms, and this group included all those with a bad outcome. Most of the differences were not statistically significant, but they analyzed admission values and minimum values obtained throughout the hospitalization separately, whereas, in our study, we compared only the extremes of values obtained within the first 48 hours of hospitalization. This may have enhanced our ability to find a difference in the two outcome groups.

Sheth et al⁴ found that in their population of 44 patients with HUS, the minimum serum Ca level for the whole hospitalization was lower in the group

Table 5.—Calcium Levels and Urine
Output as Predictors of Outcome in
Hemolytic-Uremic Syndrome*

| Test | Bad | Good | |
|-----------|---------|---------|-------|
| Result | Outcome | Outcome | Total |
| Abnormal† | 9 | 1 | 10 |
| Normal | 3 | 65 | 68 |
| Total | 12 | 66 | 78 |

*Sensitivity (9/12 patients) = 75% (47%, 91%), with 95% confidence limits; specificity (65/55 patients) = 98% (92%, 100%), with 95% confidence limits; and positive predictive value (9/10 patients) = 90% (60%, 98%), with 95% confidence limits

†Calcium level, less than or equal to 2 mmol/L; urine output, less than 0.4 mL/kg/h.

with neurologic involvement. This group included all three patients who died and the six with severe neurologic sequelae. Admission laboratory values alone were not able to distinguish between the two groups. Sheth et ald did not mention at what time during the hospitalization the minimum value occurred.

In this retrospective study of patients with HUS at CHB, we have developed a simple criterion, based only on serum Ca levels and urine output, that can be used within the first 48 hours of admission to predict the outcome of hospitalization. Because the performance characteristics of any predictive procedure tend to be optimal in the population used to define the procedure, the proposed criterion should now be applied to other populations of patients to assess its reliability as a prognostic guide.

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[†]Urine output, <0.4 mL/kg/h.

Undiagnosed Spinal Cord Injuries in Brain-Injured Children

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· Four children with brain injury were later found to have coexisting spinal cord injury (SCI). Findings that warrant investigation for coexisting SCI include a dermatome pattern sensory loss; absence of movement and reflexes in either both arms or both legs with preservation in the remaining extremities; flaccidity; absence of sacral reflexes; diaphragmatic breathing without use of accessory respiratory muscles: bradycardia with hypotension; autonomic hyperreflexia; poikilothermia; unexplained urinary retention; history of neck pain; unexplained ileus; priapism; and the presence of cionus in an unconscious patient without decerebrate rigidity. If any of the above are present, the spine should be stabilized until either further diagnostic studies confirm SCI with treatment instituted or serial neurologic examinations confirm the absence of

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Children who sustain severe brain injury may also have unrecognized spinal cord injury (SCI). Four such children 5 years of age and younger are presented. Brain injury signs and symptoms may mask those of an associated SCI; in addition, complications from high cervical injuries, such as respiratory impairment with secondary hypoxic encephalopathy, may be mistaken for a primary brain injury. The differential diagnosis of SCI as a coexisting injury with brain injury will be discussed.

PATIENT REPORTS

PATIENT 1.—A 4-year-old boy, product of a normal pregnancy, labor, and delivery, was hospitalized twice by 4 months of age for malnutrition. At 2 years of age, he was rehospitalized because of evidence of physical abuse. There were numerous scars over his entire body, including a linear scar on the neck around the right ear and under the angle of the right mandible. The abdomen and bladder were markedly distended. He moved his extremities "very little," but detailed muscle testing was not recorded.

Over the next three months, he gradually improved in muscle strength, and he was discharged from the hospital to permanent foster care. He was evaluated at ages 3 and 31/2 years, and a diagnosis of cerebral palsy was assigned to account for his quadriparesis. At age 4 years, however, SCI was first considered when it was recognized that the neurologic findings were inconsistent with cerebral palsy. Biceps deep tendon reflexes (DTRs) were normal, but radial and triceps DTRs were decreased. Patella and ankle DTRs were hyperactive, and the Babinski reflex was positive bilaterally. Voluntary movements were present in the wrist extensors and triceps, but they were absent in the hand intrinsics and lower extremities. Sensory levels could not be determined, but partial sparing of pain sensation seemed to be present in all extremities. Cervical spine roentgenograms were normal. The child was diagnosed as having C-7 quadriplegia, incomplete, with sensory sparing only, secondary to SCI due to neck trauma from suspected child abuse.

PATIENT 2 .- A 5-year-old girl who sustained a closed traumatic brain injury in a car accident had injuries that included subdural hematoma, subarachnoid hemorrhage, and a brief cardiac arrest at the scene. Cervical spine roentgenograms on the first day were normal. The question of an SCI was first considered five days after injury when she was found to have increased upper extremity DTRs but absent DTRs and decreased tone in the lower extremities. Sacral reflexes were absent. Grade 1/5 movements were observed in biceps, triceps, wrist extensors, and finger flexors bilaterally, but 0/5 movement was observed in the lower extremities. The patient remained severely cognitively impaired, limiting examination for a definite sensory level. Thoracic and lumbar spine roentgenograms revealed a fracture/dislocation of L3-4 vertebrae. Thirteen days after the injury, the patient had improved cognitive function and demonstrated grade 3/5 deltoids, 2/5 biceps, with 0/5 hand and wrist movement on the right side. On the left, the patient had grade 3/5 deltoid, biceps, and triceps with 1/5 finger flexors and extensors, and 0/5 hand intrinsics, suggesting a higher SCI. Repeated cervical spine roentgenograms now revealed a posterior subluxation of C-6 on C-7. Follow-up 15 months after injury confirmed a C-7 level quadriplegia.

PATIENT 3.—A 2-year-old girl developed progressive generalized weakness, pain in her shoulders, and nuchal rigidity over a 24-hour period. She developed respiratory

distress over the next 24 hours and required intubation and ventilatory support. Nerve conduction velocities were normal. A tentative diagnosis of encephalopathy was suggested initially because of the patient's altered mental status after the respiratory arrest and electroencephalographic findings of generalized slowing. At four days, a sensory level approximating the C-3 to C-5 dermatome was found. Deep tendon reflexes of both arms were absent with only trace DTRs in both legs. The upper extremities had no movement on the right, with grade 1/5 in the left biceps, wrist extensors, and finger flexors. There was no voluntary movement in her lower extremities. Cervical spine roentgenograms and a cervical myelogram were normal. The cerebrospinal fluid showed two white blood cells, a glucose level of 3.5 mmol/L, and a protein level of 0.79 g/L. The patient was believed to have SCI of unknown origin with encephalopathy secondary to hypoxia during the initial ventilatory failure. Two months after onset, new information suggested that the child had been struck or shaken just prior to the onset of weakness. When she was last seen at age 21/2 years, she continued to have an incomplete C-4 SCI.

PATIENT 4.—An 11-month-old girl was involved in a car accident and found at the site of the accident without spontaneous respirations. The patient was comatose on arrival at the hospital. Her neck was stiff, but cervical spine roentgenograms were normal. A head computed tomographic (CT) scan suggested diffuse edema of the right cerebral hemisphere. The primary diagnosis was traumatic brain injury with increased intracranial pressure and possible basilar skull fracture. Flaccid quadriplegia persisted two days after injury, at which time the possibility of an SCI was first considered. Except for a grade 1/5 shoulder shrug bilaterally, no voluntary movements could be found in the extremities. Only reflex withdrawal by noxious stimuli was elicited in the legs. There was no reaction to pinprick below the C-3 dermatome level and no evidence of sacral sensory sparing. Sacral reflexes were present. At age 21/2 years, she continued to have a C-3 level quadriplegia.

COMMENT

The head and spine act as highly interrelated anatomic units. Forces that cause injury to one may also damage the other. Polytrauma may result in multifocal areas of injury,

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some of which may be obscured by overlapping signs and symptoms. Brain injury, with severe neuromuscular and cognitive impairment, may obscure SCI signs, particularly in children in whom vertebral bony changes are often absent. Careful examination and appropriate radiologic studies of the spine are critical in such patients to assess and treat instability of the spine and to prevent or minimize additional loss of neurologic function.

Age is an important factor in the clinical and roentgenographic presentation of traumatic SCI. Children,1-7 like older adults,8 frequently do not have roentgenographic evidence of vertebral bony injury. Subluxation occurs, followed by spontaneous reduction without residual roentgenographic changes.9 Children normally have up to 4 mm of anterioposterior movement with pseudosubluxation, especially in flexion, at the C2-3 level and up to 4.5 mm at the C1-2 level, requiring care in positioning and caution in the interpretation of roentgenograms. 10-15

Spinal cord injury may coexist with traumatic brain injury and must be considered during initial evaluation.9,16-25 However, the diagnosis of SCI may be difficult to determine clinically, particularly when the patient presents with severe cognitive impairment. Each of the four patients presented was initially diagnosed as having brain injury with a diagnosis of SCI unsuspected until two years, 13 days, four days, and two days after injury, respectively. Maintaining stability of the spine can be critical in preventing further loss of neurologic function, and delayed diagnosis is undesirable. As seen in the following tabulation, there are certain signs and symptoms previously identified in the literature and corroborated by our experience that may suggest unsuspected SCI when brain injury dominates the clinical picture. 5,9,18,17,19,26,27

Tips on Physical Examination for SCI in Brain Injury

Myotome level motor loss
Disparity of reflexes and movement between arms and legs
Dermatome level sensory loss
Spinal shock
Absent sacral reflexes
Diaphragmatic breathing
Hypotension with bradycardia

Autonomic hyperreflexia Temperature instability Urinary retention Ileus/constipation Priapism Vertebral pain Neck muscle spasms

Some of these findings, such as spinal shock (flaccidity) or absent sacral reflexes, must be sought early in the course of injury, as they may resolve with recovery.

With both brain injury and concomitant SCI, there may be mixed sensory and motor neurologic examination findings. The examiner must be able to distinguish the three patterns of neurologic organization: (1) brain injury usually results in diffuse or regional motor and sensory loss, such as in an entire limb or one side of the body: (2) SCI usually results in a dermatome and myotome pattern; and (3) peripheral nerve injury produces more precise nondermatomal sensory and motor losses. In addition, specific muscles are innervated by specific nerves without overlap as in the first or second pattern. It is possible to see brain injury and coexistent spinal cord injury with a generalized hemiparesis on one side and myotomal loss on the other side.

Relatively normal movement with normal or hyperactive reflexes in the upper extremities and loss of movement and decreased or absent reflexes in the lower extremities warrant examination for a thoracic or lumbar SCI. 18,19,26 The loss of movement and decreased or absent reflexes in both upper extremities with normal or hyperactive movement and reflexes in the lower extremities may suggest a cervical central cord spinal injury. 5,18

Intellectual impairment from a brain injury or lack of cooperation in young children does not preclude partial mapping of the sensory response to pain, except when the patient is in a coma.17 Even in the newborn with SCI, agitation and facial grimaces may be elicited in response to pain testing in intact sensory areas.26 In incomplete SCI, the mapping of sensory dermatome levels may be more difficult. With incomplete injuries, motor loss is usually more severe than sensory loss due to the vulnerability of the larger motor fibers to trauma compared with the smaller sensory fibers.

An infant with impaired cognitive function may grimace in response to pinprick in hyposensitive areas, suggesting that sensation is intact. However, when the patient develops communication skills, he may describe subtle differences in sensation that allow more accurate mapping of dermatome levels. The lack of a response to pinprick is a strong indicator of impaired spinal function in those with impaired intellectual response, but the presence of a response to pinprick does not preclude incomplete SCI.

Spasticity usually develops rapidly after brain injury, whereas a period of decreased tone ("spinal shock") manifested by flaccidity and absent reflexes below the level of injury may be present with SCI. ^{13,17,26} Movement of limbs in response to pain in a braininjured patient may not rule out SCI. After the period of spinal shock, nonvoluntary spinal reflex activity may return. ¹³ Care must be taken to distinguish disinhibited reflexes from voluntary movements.

The bulbocavernosal and anal reflexes are present at all times in the patient who has sustained a brain injury but may be absent during the early stages of SCI.¹³ These reflexes may be absent permanently when the SCI is in the area of the conus medullaris or cauda equina, which results in lower motor neuron paralysis.¹³ The absence of sacral reflexes should suggest the possibility of an SCI.

Spinal cord injury in the cervical region may involve the origin of the phrenic nerve leading to respiratory failure. A history of cardiorespiratory arrest after a traumatic injury followed by hypoxia and coma may be mistakenly attributed to brain injury or encephalopathy.22 Silver et al22 reported that of 100 spinal injuries in patients 11 to 70 years of age, the most commonly associated injury was brain injury, occurring in 50% of the patients. They also noted a paradox in that there were fewer brain injuries in patients with cervical SCI but more often brain injury was found in patients with thoracolumbar SCI.22 They speculated that this may reflect a natural selection of patients, since cervical spine injuries combined with brain injury often lead to respiratory depression and death at the scene of the accident.22 Brain injury with lowerlevel SCI allows sufficient respiratory reserve for survival until medical assistance occurs. Silver et al also noted that cervical or thoracic SCI associated with brain injuries may present with confusion or cerebral edema from hypoxia rather than from brain injury. Diaphragmatic breathing in an unconscious patient should make one suspect an SCI. In a cervical or high thoracic SCI, breathing may only be diaphragmatic, while patients with brain injury use all muscles of respiration.

Decreased blood pressure combined with tachycardia during the early stages after injury suggest surgical shock. Decreased blood pressure associated with bradycardia suggests SCI above the T-6 level with interruption of the sympathetic outflow, otherwise known as spinal shock. 18,17,19,27 Episodes of unexplained blood pressure elevation, particularly if associated with bradycardia, with flushing and sweating above the injury level. may suggest a spinal cord lesion above T-6 resulting in autonomic hyperreflexia. 13,17,27 Patients with brain injury may also show signs of autonomic dvsfunction, including sweating and flushing of the face and upper part of the chest or sustained blood pressure elevation, but they usually do not have associated bradycardia or intermittent elevation in blood pressure. Unusual temperature instability, poikilothermy, may suggest spinal cord lesion due to loss of the autonomic mechanism for vasoconstriction, vasodilation, or shivering. 13,26

A variety of other signs and symptoms may suggest SCI. Prolonged urinary retention should raise suspicion of SCI with neurogenic bladder. 18,17,19 Prolonged unexplained lack of fecal emptying in the person with brain injury may be the result of a neurogenic bowel from SCI.18,17 Priapism is common after SCI, but it is rare after brain injury. 18,17 Pain over the vertebrae, especially with a history of neck pain or limitation of lateral neck motion after traumatic injury, warrants closer evaluation.9,17 Presence of clonus without decerebrate rigidity may suggest SCI. 19

Delayed onset with progression of neurologic impairment may mistakenly be attributed to some other neurologic disorder.^{2-5.7} This delayed loss occurs with some frequency in children during the first four days after injury.^{2-5,7} Patient 3 demonstrated this picture of progressive myelopathy that was not recognized as SCI until four days after onset.

If any of the above findings are present in the traumatic brain-injured patient, or if cognitive impairment precludes an adequate neurologic examination, the patient should be treated as though there is spinal instability, ie, with log roll, cervical collar, skeletal traction. For the brain-injured child with suspicion of SCI, we concur with the evaluation for SCI as outlined by Hadley et al.6 Plain roentgenograms of all suspicious areas for injury, including a full spinal column assessment, are first recommended. followed by CT scanning of specific regions in question.6 If no fracture or subluxation is found, then dynamic physician-controlled lateral cervical spine flexion-extension roentgenograms to assess spinal ligamentous instability should be considered.3,6 Computed tomographic-metrizamide myelography is reserved for neurologic deficits unexplained by the previous studies or for further classification of precise impingement of the cord.6 Magnetic resonance imaging may be a promising alternative to CT scanning and dynamic views, though the evidence of its superiority over other imaging technologies is still to be defined. 6,28 Logistics problems with providing cardiopulmonary support for the unstable patient and instrumentation such as traction devices during short-term evaluation may limit accessibility to magnetic resonance imaging.28 The diagnosis of SCI ultimately rests on physical findings and clinical course, as SCI can be present even when results of all studies are normal. The physical examination must influence the treatment. When equivocal, the spine should be stabilized until SCI is ruled out by serial neurologic examinations.

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Life Span of Intravenous Cannulas in a Neonatal Intensive Care Unit

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 Peripheral intravenous cannula use in a neonatal intensive care unit was surveyed prospectively to ascertain the rate of complications and the factors influencing the life span of an intravenous cannula. During a three-month period in which 199 intravenous cannulas were inserted in 69 patients, only two significant infiltrations (1%) were observed in more than 5000 hours of intravenous therapy. None of the factors studied, including weight, age, type and rate of fluid administration, and type of medication (except pancuronium bromide), had any discernible effect on the functional life span of intravenous cannulas. Pancuronium was associated with a significant prolongation of cannula life span-from 30 to 50 hours. We conclude that in this setting, the rate of clinically significant complications from intravenous cannula therapy is low.

(AJDC 1988;142:968-971)

The use of peripheral intravenous cannulas (IVCs) in the provision of neonatal intensive care is a commonly accepted practice. Although IVC use is essential for administration of medication, dextrose, and fluids, potentially serious complications may arise. Infiltrations may lead to sloughing of skin severe enough to require skin grafting or may result in loss of function.

Current incidence rates of complications associated with peripheral IVCs in this setting are unknown. Accordingly, we designed a prospective survey of IVC use in the University of Michigan Holden Neonatal Intensive Care Unit, Ann Arbor. Our objectives were twofold: to define the incidence of complications of IVCs in

our nursery population and to assess factors that might influence the life span of IVCs, which we defined as the number of hours that an IVC remains functional from the time of insertion until removal.

PATIENTS AND METHODS

We prospectively surveyed all newborns receiving a peripheral IVC during the three-month period from December 1985 through February 1986. During this time, there were 115 admissions to the neonatal intensive care unit (NICU). Sixty-nine infants received IVCs that were inserted, observed, and withdrawn while they were in the NICU. The total number of IVC procedures observed was 199. The only exclusions from the survey were patients whose peripheral IVCs were not inserted, observed, and withdrawn while they were in the NICU and patients receiving extracorporeal membrane oxygenation. In the latter category, patients receive systemic heparin sodium therapy, and their IVCs are not removed when infiltration is suspected but are capped and removed only when extracorporeal membrane oxygenation has concluded. This survey did not include patients with central IVCs, such as Broviac catheters, umbilicoarterial catheters, and umbilicovenous catheters, unless the patients also had peripheral IVCs.

At the University of Michigan Holden Neonatal Intensive Care Unit, nurses insert virtually every IVC. An IVC is withdrawn when it is no longer needed or when the nurse believes that it either is no longer functional or is producing complications. The nurses do not routinely change intravenous sites after any specified number of hours.

Skin is prepared with povidone-iodine and alcohol. Antibiotic ointment is not usually placed on the site, and no occlusive dressings are used (Fig 1). Twenty-four-gauge Teflon over-the-needle IVCs are used almost exclusively. Only one stainless-steel scalp-vein needle was used during the survey period.

Infusion pumps are used for all IVCs,

and blood products are administered by syringe pumps; gravity drips are never used. Heparin sodium is not added to intravenous fluids, except in parenteral nutrition solutions, where it is used in a concentration of 1.0 U/mL. Hydrocortisone is not added to intravenous solutions.

Nurses were not informed that this survey was taking place, and the documentation used for the survey was data that were routinely charted on the daily patient flowchart as a matter of unit policy. For each IVC procedure, patient weight at the time of IVC placement, gestational age corrected for postnatal age, and diagnoses were recorded. Daily data collected for each IVC included site, average fluid administration rate and any fluid bolus given, average glucose infusion rate in milligrams per kilogram of body weight per minute, and all medications used (which were recorded separately). Rather than simply noting the use or nonuse of a particular medication during the life of an IVC placement, we assigned a weighted fraction as follows: the number of days in which medication was used divided by the IVC life span in days. This designation allowed greater detail in the assessment of factors influencing IVC life span or complications. Additional details recorded were parenteral nutrition solutions and blood products used. Details of timing of placement and removal of IVCs allowed for calculation of IVC life span in hours.

Complications that appeared to be related to the IVC were recorded. Also noted were criteria for discontinuation of the IVC procedure and whether the cannula was electively removed or withdrawn because of redness, swelling, leakage, or inability to flush. The term *infiltration* was used generically to describe the group of reasons that an IVC was considered to be nonfunctional.

Because the distribution of IVC life spans was nonnormal, nonparametric statistical tests were used. The Mann-Whitney U test was used to compare groups. (Statistical significance was achieved if $P \le .05$.) The IVC life span was also expressed by life-table analysis. Time of infiltration was

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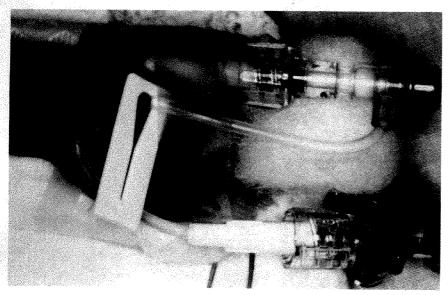


Fig 1.—Typical peripheral intravenous cannula in use.

analogous to time of death. Elective discontinuation of an IVC procedure corresponded to withdrawal from the study. Life-table analysis then provided cumulative survival curves. The IVC life span was grouped by patient or IVC characteristics and examined separately with life-table analysis. Breslow's test was used to compare survival curves.

RESULTS

Sixty-nine patients received 199 cannulations that met survey criteria. Of the 199 total IVCs, 125 (63%) became infiltrated and 74 (37%) were electively withdrawn. A total of 5007.5 hours of IVC use were observed. Figure 2 shows the distribution of all IVCs by postconceptional age. Figure 3 displays the frequency distribution of all IVCs by the number of hours each IVC functioned. Median IVC life span for the entire group was 33 hours. Figure 4 shows IVC life span by lifetable analysis as a survival curve.

In an examination of factors that might influence IVC life span, no statistically significant differences were found for the extreme ranges of the following variables: weight at the time of IVC placement (<1500 to >3000 g); postconceptional age (<32 to >40 weeks); infusion rate of fluid (<70 to >150 mL/kg/d); or infusion rate of glucose (<6 to >12 mg/kg/min). To examine medications possibly associated with IVC infiltration, we separated IVCs not used for medication from IVCs whose calculated fraction

exceeded 0.5. Using this grouping, we found no significant differences in IVC duration associated individually with morphine sulfate, phenobarbital sodium, ampicillin sodium, or gluconate calcium. Data were not analyzed for combinations of medications. No significant differences were associated with the use of parenteral nutrition solutions, blood products, or pressor agents. However, pancuronium, a skeletal muscle relaxant, was associated with a significant difference in IVC life span (P = .05). Median life span in patients not receiving this medication was 30 hours, whereas the duration was 50 hours in patients who received it (Fig 5).

During the survey period, only two (1%) of 199 cannulations were associated with significant complications. The first instance occurred in a 1.68-kg infant at 47 hours of IVC life. The infant was receiving dopamine hydrochloride via the IVC. The second occurred in a 3.86-kg infant at 61 hours. Medications received were ampicillin, gentamicin sulfate, phenobarbital, pancuronium bromide (Pavulon). morphine, and sodium bicarbonate. In each case, sloughing of the skin required the topical use of antibiotics, and neither skin grafting nor surgical intervention was necessary. Therefore, only two instances of significant complications were observed during a 5000-hour period of IVC use. Such a low incidence rate precluded us from

assigning associated risk factors for local complications of IVC infiltration. Although our survey did not include routine culturing to assess local bacterial colonization or systemic infection, we encountered no instance of bacteremia attributed to IVC use.

COMMENT

Peripheral IVC use in the NICU is commonplace, yet a number of associated problems exist, including IVC infiltration and subsequent sloughing of the skin. Previous reports have shown the potential seriousness of IVC-related sloughs. Yosowitz and colleagues1 described six infants with skin sloughing, four of whom required grafting. Details of intravenous access were not mentioned. Cutaneous necrosis associated with intravenous use of nafcillin sodium was observed by Tilden and coworkers.2 Three of the four infants in their report had received scalp-vein needles. Two cases of necrotizing fasciitis of the scalp in newborns were described by Gibboney and Lemons.3 The lesions were large and very slow to heal; one required a skin graft.

The only reports commenting on the frequency of IVC-related sloughs do not clearly specify the type of IVC used. Collinge and Aranda reported on a six-month experience in a regional NICU. Among 200 admissions were 133 infants who received intravenous therapy for longer than 24 hours. Sixty-one (46%) of these infants had at least one complication related to therapy. Sloughs were seen on 217 occasions in 58 infants. A startlingly high average of 3.7 sloughs per infant (range, one to 26) was reported. They did not report IVC life span but did comment that few stayed in situ longer than 24 to 36 hours. Chandavasu and associates reported a rate of two or three skin sloughs a week but did not state whether stainless-steel needles or Teflon cannulas were used in their unit, nor did they report details of IVC life span. Phelps and Helms⁶ studied a group of infants up to 8.7 months of age who received either Teflon cannulas or steel needles. Using stepwise Cox regression analysis, they examined multiple variables for potential risk of infiltration. In their study of

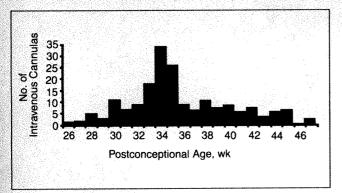


Fig 2.—Distribution of intravenous cannula use by postconceptional age.

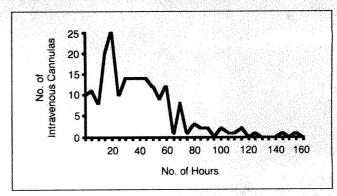


Fig 3.—Frequency distribution of intravenous cannula life span.

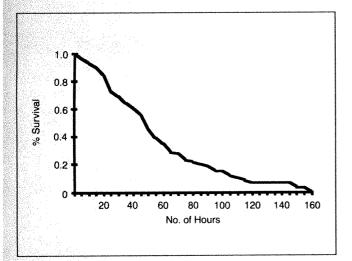


Fig 4.—Survival curve for intravenous cannula use determined by life-table analysis.

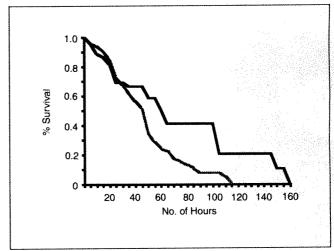


Fig 5.—Comparison of survival curves for intravenous cannulas with and without pancuronium use. Lighter line represents no pancuronium use; heavier line, cannulas in which weighted fraction of pancuronium use exceeded 0.5.

151 infusions, they observed no episodes of skin sloughing or tissue necrosis related to intravenous infiltration. The total number of hours of intravenous use observed was not stated.

Treatments to lessen the severity of IVC-related sloughs have been reported anecdotally. Gentle massage of the infiltrated area, multiple punctures over the area of infiltration, and medications such as hyaluronidase have been proposed.

The methods of obtaining intravenous access in newborns have changed over the years in an attempt to lessen complications and ensure reliable lines. Stainless-steel scalp-vein needles were the initial standard. In many institutions, these have been abandoned in favor of Teflon IVCs. The controlled study of Batton and

colleagues⁹ demonstrated that the functional life span of 24-gauge Teflon cannulas was longer than that of 25-gauge stainless-steel needles. Among 58 IVCs, the average life span was 15.4 hours for 28 stainless-steel needles, compared with 49.5 hours for 30 Teflon cannulas. No mention was made of skin sloughs.

Centrally or peripherally placed catheters may be inserted by direct cutdown or percutaneously for long-term access. Recently, there has been a renewed interest in these catheters. 10,11 These lines are also not without risk. Complications such as sepsis, perforation, vascular scarring, arrhythmias, hypoglycemia, emboli and thrombus formation, and malposition have been reported. 12-15 Before changing to new policies of IVC infusion, we chose to prospectively define the cur-

rent complication rate in our NICU. It is hoped that institutions gaining experience with alternative IVC use will also perform comparison studies to determine relative risk-benefit ratios of different methods of intravascular access.

The potential cosmetic and medicolegal concerns arising from IVC infiltrations also served as an impetus for the determination of catheter-related injuries. The low incidence rate suggests that a policy of routinely changing IVCs after a specified number of hours of use may be unwarranted and in fact may subject the infant to unnecessary stress. We attribute our low incidence of IVC complications to the policy of IVC placement and removal by the neonatal nurses. To confirm this hypothesis, we are analyzing data collected five years ago, when

IVC placement was performed almost exclusively by the house officers. The longer life span of IVCs in patients receiving pancuronium is probably not a specific effect of that medication but rather a consequence of the neuromuscular paralysis-preventing motion of the IVC. Observing IVC life span in patients with paralysis might substantiate this speculation.

Factors that influence IVC life span

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Phelps SJ, Helms RA: Risk factors affecting infiltration of peripheral venous lines in infants. could have been missed because of an insufficient number of subjects in the examination of specific medications. Since our survey was designed to calculate the incidence of IVC complications, we could not prospectively determine the number of subjects required to demonstrate significant effects of individual medications. Given the low incidence of complications, an enormous study population

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would be required to examine this aspect in more detail.

We conclude from this prospective survey of patients in the NICU that the rate of clinically significant IVC infiltrations is very low. Furthermore, IVC life span may be independent of multiple factors, with the exception of pancuronium use, which appears to prolong IVC life span.

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In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY-HEAD & NECK SURGERY
Screening for Auditory Dysfunction in Infants by Evoked Oto-Acoustic
Emissions

Pierre Bonfils, MD; Alain Uziel, MD, PhD; Rémy Pujol, PhD (Arch Otolaryngol Head Neck Surg 1988;114:887-890)

Usefulness of Serum Thyrotropin-Binding Inhibitory Index Measurements in Infantile Hypothyroidism

Relationship to Serum Thyrotropin Concentrations

Dorothy I. Shulman, MD; John A. Strzelecki, MT; Barry B. Bercu, MD; Allen W. Root, MD

• Transplacental passage of thyrotropin (TSH)-binding inhibitory immunoglobulins may result in transient congenital hypothyroidism. We measured serum TSH-binding inhibitory index (TBII) in 11 infants with abnormal screening findings using a commercially available kit. Two of the infants, who were siblings, had markedly elevated TBII values (90% and 100%, respectively), as did their mother (89%, 100%), and had a clinical course consistent with transient antibody-mediated hypothyroidism. Four other infants had a borderline or mildly elevated TBII that was not present in maternal serum, suggesting that endogenous TSH was being measured in this assay. The TBII was measured in the sera of 18 additional children with primary hypothyroidism and in human TSH standards from 25 to 2000 mU/L. Increasing concentrations of TSH were associated with a linear increase in TBII. Measurement of TBII by this method may identify infants with transient antibody-mediated hypothyroldism, although simultaneous assessment of maternal serum is necessary. (AJDC 1988;142:972-974)

With the establishment of screening programs in newborns for infantile hypothyroidism, much information has been gathered regarding the incidence and pathogenesis of this disease. Infantile hypothyroidism in

North America occurs in one in 4000 infants,1 and is transient in approximately 10% of affected infants.2 Recognized causes of transient hypothyroidism include maternal iodine deficiency, excessive exposure of the fetus or neonate to iodine, maternal ingestion of propylthiouracil and related drugs, and transplacental passage of thyrotropin (TSH)-binding inhibitory immunoglobulins. Matsuura and coworkers3 described transient congenital hypothyroidism in two offspring of a woman with nongoitrous autoimmune hypothyroidism in whom there was transplacental passage of immunoglobulins that inhibited TSH binding to thyroid membranes and blocked TSH-induced cyclic adenosine monophosphate generation in murine thyroid tissue. The TSH-blocking immunoglobulins disappeared from the serum of both infants by 6 months of age, and they remained euthyroid after discontinuation of thyroid hormone supplementation. Similar case reports have followed.4-7

We recently began to look prospectively for evidence of TSH-binding inhibitory immunoglobulins in neonates with abnormal screening findings using a commercially available kit. We found that elevated endogenous TSH levels may result in a falsely elevated TSH-binding inhibitory index (TBII) by this method. Measurement of simultaneously elevated TBII values in infant and maternal sera, however, may identify those infants in whom antibody-mediated congenital hypothyroidism is likely to be present.

PATIENTS AND METHODS

Eleven infants referred for low screening thyroxine (T₄) values (<10th percentile on

a given day) and elevated TSH values (20 mU/L) were examined, and serum was collected for measurement of T₄, triiodothyronine resin uptake, TSH, antimicrosomal and antithyroglobulin antibodies, and TBII. The mothers were simultaneously studied.

Thyrotropin-binding inhibitory index was measured using a commercially available radioassay kit (Clinetics Corp, Tustin, Calif). This kit is designed and marketed for measurement of thyroid-stimulating immunoglobulins in sera of patients with Graves' disease. The assay was performed by combining a 50-µL aliquot of the patient's serum with an aliquot of porcine TSH receptors. After a 15-minute incubation at room temperature, human tracer TSH was added, which competes with serum factors that might bind to the TSH receptor. After a 60-minute incubation at 37°C, the TSH receptor complex was precipitated with polyethylene glycol. The radioiodine in the precipitate was counted and compared with the total counts in the assay, negative control serum, and positive control serum. The TBII was calculated using the following formula: (1-% receptor bound iodine 125-labeled TSH/% maximum binding) × 100. It describes the percent inhibition of binding of radiolabeled TSH from TSH receptors compared with that in normal control serum. Less than 10% is considered negative, between 10% and 14% is indeterminant or borderline, and greater than 14% is considered positive. This assay does not distinguish the biologic activity of the serum factor (stimulatory or inhibitory) that is competing for labeled TSH binding, nor is it specific for immunoglobulin. Presumably, any serum factor that binds to the TSH receptor can result in an elevated TBII. To assess the effect of TSH on the TBII, the TBII also was measured in sera from patients with high endogenous TSH values and after addition of standard TSH to the TBH assay.

Thyroxine and TSH were measured by radioimmunoassay kits (NML Products,

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of South Florida College of Medicine, Tampa, and All Children's Hospital, St Petersburg, Fla. Read in part before the Society of Pediatric Research, Anaheim, Calif, April 29, 1987.

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Infant Serum TBII and TSH
Measurements and Maternal Serum
TBII Values in 11 Infants With
Congenital Hypothyroidism at Time
of Diagnosis*

| | infa | nt | |
|---------|--------------|-------|------------------------|
| Patient | TSH, mU/L | TBII, | Mother's TBII, % |
| 1† | 593 | 90 | 89 |
| 2† | 211 | 100 | 100 |
| 3 | 508 | 18 | 5 |
| 4 5 | 549 | 15 | 7 |
| 5 | 603 | 2 13 | 1 |
| 6 | 150 | 12 | 7 |
| 7 | 64 | 9 | 9 |
| 8 | 610 | 7 | 3 |
| 9 | 7 | 7 | 5 |
| 10 | 12 | 5 | 5 |
| 11 | 30 | 3 | 1 |

*TBII indicates thyrotropin binding inhibitory index; TSH, thyrotropin.

†Patients 1 and 2 are siblings

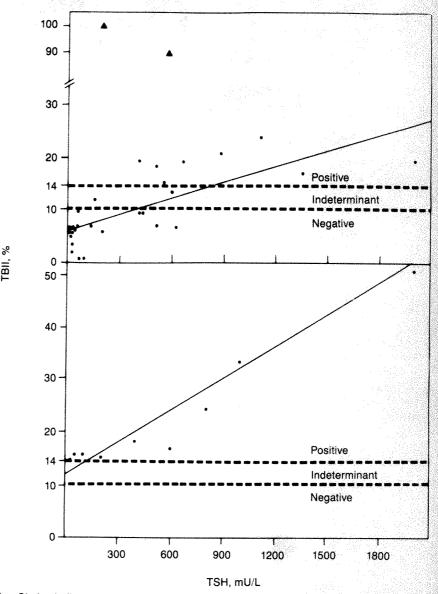
Organon Teknik Corp, Irving, Tex, and Hybritech, San Diego, respectively) in the All Children's Hospital (St Petersburg, Fla) Pediatric Endocrinology Laboratory. Antimicrosomal and antithyroglobulin immunoglobulins were measured by serial dilution and hemagglutination (Wellcome Diagnostics, Research Triangle Park, NC).

Linear regression was used to calculate the coefficient of correlation between TSH and TBH values.

RESULTS

Serum TSH and TBII measurements in the 11 infants and TBII values in their mothers are shown in the Table. All mothers were biochemically euthyroid at the time of serum sampling.

Patients 1 and 2 are siblings. Patient 1 was a firstborn term male infant with screening T4 and TSH levels of 81 nmol/L and 397 mU/L, respectively. Birth weight was 4.1 kg and length was 55 cm. When he was 14 days old, his serum T4 level was 49 nmol/L and TSH level was 593 mU/L. The infant had no clinical signs of hypothyroidism. Technetium Tc 99m scan revealed absence of the thyroid gland. Bone age was consistent with a term infant. The mother had a six-year history of nongoitrous autoimmune hypothyroidism and was currently receiving T4 therapy. Elevated titers of serum antimicrosomal (1:1600) and antithyroglobulin (1:320) antibodies were present in the mother and infant. The



Top, Circles indicate simultaneous thyrotropin (TSH) levels and thyrotropin-binding inhibitory index (TBII) values from sera of 27 children with primary hypothyroidism and elevated TSH values (r=.72, P<.001); triangles, two infant siblings with transient TSH-blocking antibody-mediated hypothyroidism. Bottom, TBII values measured in varying concentrations of human TSH standard (r=.97, P<.001).

TBII was markedly elevated in maternal and infant serum (89% and 90%, respectively). Thyroxine therapy was initiated in the infant. At age 3.5 months, the infant was euthyroid (TSH level, 4.4 mU/L; T₄ level, 164 nmol/L), but serum TBII remained elevated (89%). By 7 months of age, antithyroid antibody titers and TBII had declined to undetectable levels in the infant but remained elevated (TBII, 94%) in the mother. Thyroxine therapy was discontinued in the infant at 2 years of age and did not result in recurrence of the hypothyroid state

(serum T₄ level, 129 nmol; TSH level, 4.8 mU/L). A repeated technetium Tc 99m scan at 2.5 years of age revealed the thyroid gland to be of normal size and position. The mother again became pregnant. Cord blood T₄ and TSH values in the second-born child (patient 2) were 89 nmol/L and 211 mU/L, respectively. The TBII was 100%, identical to a simultaneous serum measurement in the mother. This full-term female infant had a birth weight of 3.0 kg, a length of 48 cm, and no clinical signs of hypothyroidism. Thyroxine therapy was initiated

on day 1 of life. Elevated titer antimicrosomal (1:400) and antithyroglobulin (1:320) antibodies and TBII became undetectable by 7 months of age. Thyroxine therapy was discontinued at age 12 months. The infant has remained euthyroid (T 125 nmol/L; TSH level, 3.4 mU/L). Iodine 123 uptake and scan at age 1.5 years revealed a normal thyroid gland. Developmental milestones have been reached appropriately in both children.

Four of the other nine infants tested had borderline or elevated TBII values not present in maternal serum. The infants with borderline or positive TBII values also had the highest TSH concentrations, suggesting that excessive TSH levels might be falsely elevating the TBII measurement. To adquestion. TBII dress this determined in frozen serum from 18 other children with primary hypothyroidism in whom elevated TSH concentrations had been measured previously. There was a significant positive correlation between TSH concentrations and TBII (r=.72, P<.001) (Figure, top). Thyrotropin values greater than 150 mU/L were likely to be associated with a borderline or mildly positive TBII. Repeated measurements of TBII in the serum of three children, obtained three to six months after suppression of TSH concentra-

tions with exogenous thyroid hormone, were clearly negative.

The TBII values of the two siblings with transient congenital hypothyroidism mentioned previously are represented by the two triangles at the top of the top portion of the Figure. Their TBII values were much higher than values found in the serum of the other hypothyroid children and did not become normal immediately after normalization of serum TSH concentrations. Their data are excluded from the correlation statistics.

Concentrations of human TSH standard (first international reference preparation) provided by the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases ranging from 25 to 2000 mU/L in buffer were also evaluated in the TBII assay (Figure, bottom). Increasing concentrations of TSH were associated with a linear increase in TBII (r=.97,P < .001).

COMMENT

Transplacental passage of TSHbinding inhibitory immunoglobulins may be responsible for transient infantile hypothyroidism in some newborns. Measurement of TBII is a readily available procedure that may identify such infants and allow for early identification of affected siblings. Simultaneous measurement of TBII in maternal serum appears to be essential, however, because elevated TSH concentrations in the infant may falsely increase TBII values. Measurement of TBII should be considered in all newborn infants with elevated TSH values as a potential marker of transient immunologically mediated disease. This test is recommended particularly for hypothyroid infants with a maternal history of thyroid disease.

A role for immunoglobulins interfering in the normal development of the fetal thyroid gland has been proposed by Van der Gaag et al,8 who recently reported the presence of immunoglobulins blocking TSH-induced thyroid growth in the serum of 15 of 34 mothers of infants with infantile hypothyroidism. On radioisotopic scanning, four infants of mothers with thyroid growth-inhibiting immunoglobulins had ectopic thyroid tissue, suggesting that immunoglobulins may play a role in dysgenetic as well as transient hypothyroidism. It is unclear whether the TBII assay used in our small study can serve as an effective screen for such immunoglobulins. Further studies using this assay as well as more specific bioassays in a larger number of infants with infantile hypothyroidism of various causes are necessary to understand the role of immunoglobulins in this condition.

The authors thank Mrs Valarie Collins for secretarial assistance.

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Quotables:

Predictions: It is difficult to make predictions—particularly about the future.

CONFUCIUS

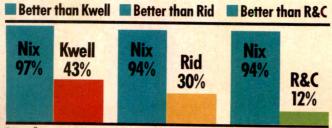
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INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus* var. *capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of in vitro and in vivo genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly recorded.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp. Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic or other reasons.

SHAKE WELL BEFORE USING.

HOW SUPPLIED: Nix (Permethrin) 1% (wt./wt.) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g. (NDC-0081-0780-81) Store at 15°-25°C (59°-77°F).

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Special Features

Radiological Case of the Month

Beverley Newman, MD (Contributor); Lionel W. Young, MD (Editor for This Case); Beverly P. Wood, MD (Section Editor)

A 3120-g, full-term female newborn was born to a 31-year-old mother following an uncomplicated pregnancy, labor, and delivery. The newborn's initial Apgar scores were 4 and 6 at one and five minutes, respectively, and she had mild respiratory distress and transient hypoglycemia. These problems resolved in approximately two hours, and medically the neonate seemed normal enough to receive her first oral feeding after 12 hours of age. At 20 hours of age, she suddenly became hypotensive and cyanotic, while abdominal distention and profound shock rapidly followed. A sepsis workup was begun and an abdominal roentgenogram (Figure) was obtained. Hypotension persisted despite aggressive medical management, and emergency laparotomy became necessary. Thirtysix hours later the newborn died. An autopsy limited to the chest and abdomen ensued.

Accepted and edited for publication by Lionel W. Young, former section editor, Oct 16, 1986.
From the Department of Radiology, Children's Hospital of Pittsburgh.

Reprint requests to Department of Radiology, Children's Hospital Medical Center of Akron, 281 Locust St, Akron, OH 44308 (Dr L. W. Young).

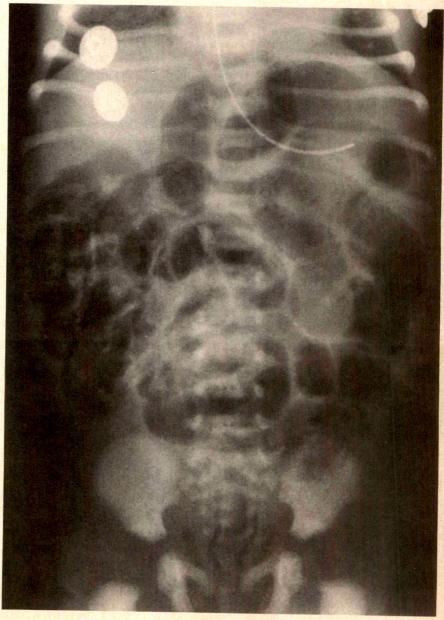


Figure.

Denouement and Discussion

Necrotizing Enterocolitis and Congenital Adrenal Hypoplasia

Abdominal roentgenogram demonstrates distention of bowel loops. Intramural gas extends throughout small bowel, large bowel, and rectum.

At operation, necrotizing enterocolitis was found affecting the bowel from the duodenum to the anus. There was no evidence of mesenteric arterial or venous thromboembolism. At autopsy, the extensive necrotizing enterocolitis was confirmed. There also was marked hepatic necrosis and acute tubular necrosis of the kidneys. An unexpected finding was that of severe congenital adrenal hypoplasia. The combined adrenal weight was less than 1 g; the normal combined weight should have been approximately 8 g.

Necrotizing enterocolitis is usually seen in sick premature newborns around the first week or two of life. Sick full-term newborns account for 20% of newborns with necrotizing enterocolitis.1 These patients usually have an underlying abnormality, such as cyanotic congenital heart disease, prolonged diarrhea, or polycythemia, or have undergone surgical operation.1-8 However, a number of apparently normal full-term newborns with necrotizing enterocolitis also have been described.24

The etiology of necrotizing enterocolitis is unclear but probably multifactorial. There is usually a history of oral feeding that presumably allows colonization of the gastrointestinal tract. Hypoxia or hypotension is thought to stimulate a physiologic dive reflex that causes selective shunting of blood away from the bowel to the heart and brain. Such shunting of blood leads to the gastrointestinal ischemia and mucosal injury that triggers the development of necrotizing enterocolitis.5,6 The distal ileum, cecum, and ascending colon are the most common sites of involvement, while the stomach is affected occasionally, and lesions of the

duodenum and rectum are rare.4

Roentgenographic findings may be varied.5,7 The most common finding is nonspecific general bowel dilatation.7 There may also be diminished bowel gas with irregular bowel loops. However, a persistently dilated and unchanging bowel loop is often gangrenous. In the clinical setting of necrotizing enterocolitis, intramural air is excellent confirmatory evidence of the diagnosis. Nevertheless, in some instances intramural gas may be difficult or impossible to distinguish from intraluminal fecal material. The extent and persistence of intramural gas does not correlate with the severity of the disease. Portal venous gas may be a consequence of this condition, but it does not necessarily predict a poor outcome. The presence of free peritoneal gas and/or liquid indicates that bowel perforation has occurred.

In this newborn, the early respiratory distress and hypoglycemia, as well as the fulminating nature of the necrotizing enterocolitis, are explicable on the basis of the unexpected autopsy finding of congenital adrenal hypoplasia. Because this is a rare disease, prospective clinical diagnosis is seldom made. The diagnosis becomes apparent only after autopsy.8 The cardinal clinical features are hypoglycemia, hyponatremia, and unexplained shock.

Clues in the prenatal history to suggest a fetus with adrenal hypoplasia include maternal preeclampsia and decreased maternal urinary estriol levels. Frequently, the fetus is small and the pregnancy extends beyond the due date.9 None of these factors was present in our case. The infantile type of adrenal hypoplasia usually presents in the first few days of life, is thought to be an autosomal recessive condition. and is frequently associated with inabnormalities, ranging tracranial from anencephaly to pituitary abnormalities. Unfortunately, permission was not obtained to examine the intracranial contents in this case. When clinically recognized, congenital adrenal hypoplasia is eminently treatable.

This case emphasizes that necrotizing enterocolitis may occur in full-term newborns, that signs and symptoms may be fulminating, and that an underlying cause is often recognizable. In this case, adrenal hypoplasia was the cause of profound shock that probably precipitated necrotizing enterocolitis. This association has not, to our knowledge, been reported previously.

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The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Beverly P. Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Radiological Case of the Month

Robert S. Baker, MD, Steven J. Goldstein, MD (Contributors); Lionel W. Young, MD (Editor for This Case); Beverly P. Wood, MD (Section Editor)

Accepted and edited for publication by Lionel W. Young, former section editor, April 29, 1987. From the Departments of Ophthalmology and Pediatrics (Dr Baker) and Diagnostic Radiology (Dr Goldstein), Albert B. Chandler Medical Center, University of Kentucky, Lexington.

Reprint requests to Children's Hospital Medical Center of Akron, 281 Locust St, Akron, OH 44308 (Dr L. W. Young).

A 15-year-old girl was examined for right-sided ocular proptosis that had been gradually progressive over a one-year period. Her right eye bulged approximately 0.5 cm and was oriented medially and slightly downward. She had no pain or tenderness. Visual acuity was 20/20 OU and visual

fields were full, with no diplopia in any field of gaze. Results of neurologic and physical examinations were normal.

The orbits were examined by complex motion tomography (Fig 1) and computed tomography (Fig 2). The right orbit was surgically explored through a lateral approach.

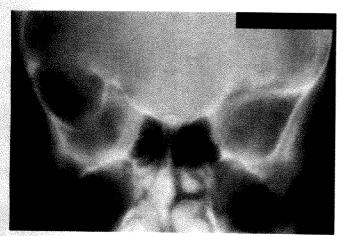


Figure 1.

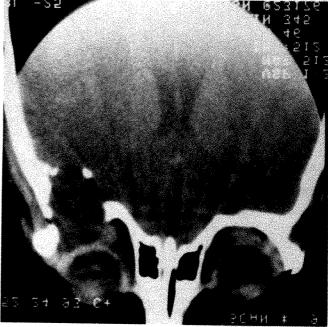


Figure 2.

Denouement and Discussion

Epidermoid Cyst of the Orbit

Fig 1.—Frontal complex motion tomogram of orbits shows cystic expansile lesion of orbital roof of right globe. Lesion has eroded inner table of skull and inferiorly displaced orbit.

Fig 2.—Coronal computed tomogram of orbits shows low-density lesion eroding orbital roof, superiorly displacing dura, and inferiorly pushing right globe and adjacent orbital contents.

Fig 3.—Section of cyst wall shows epithelial lining (arrow) and enclosing keratinaceous debris (hematoxylin-eosin, original magnification × 165).

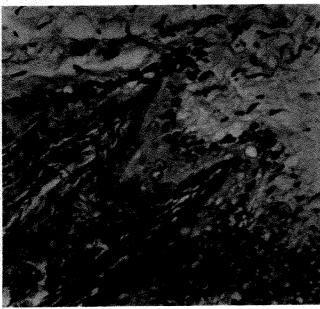


Figure 3.

A gray, cystic mass was found on surgical exploration of the right orbit via a lateral approach, without excision of bone. The lesion, limited by periosteum below and dura above, was totally removed by stripping it away from surrounding tissues. Postoperatively, right-sided ocular proptosis resolved.

Benign, progressively expanding dermoid or epidermoid cyst of the orbit may grossly deform bone and displace the eye.1 The terms dermoid cyst and epidermoid cyst should replace the older term cholesteatoma. However, these orbital cysts should not be confused with the developmental solid dermoid that is found on the surface of the eye.2

The dermoid cyst is the most fre-

quently encountered orbital mass lesion in childhood.3-6 It usually presents as a visible mass in the superolateral aspect of the orbit.1 Such a cyst, arising deeper in the orbit, as in our case, may present with exophthalmos, ptosis, and limited mobility of the eye. The cyst consists of a fibrous capsule lined by epithelium in the epidermoid type and epithelium and deeper skin structures, such as sebaceous glands and hair follicles, in the dermoid type. The center of the cyst in both is filled with epidermis-produced keratin, cholesterol, and desquamated epithelial cells, as in our case (Fig 3). The lesion is usually attached to periosteum by a short stalk.2

As the cyst slowly enlarges, bone under or over the lesion undergoes pressure erosion. The deep orbital lesion originates in the diploetic space, displaces bone and dura to the cranial cavity, and pushes orbital periosteum to the cavity of the orbit. Our case is an example of this pattern of growth.

Dermoid and epidermoid cysts are congenital. Only a few are present at birth—they are usually diagnosed between 3 and 10 years of age.2 These cysts are thought to represent a sequestration (dermal inclusion) of surface ectoderm in the deep structures of the orbit at some unknown time during fetal life. This theory has as its basis the close approximation of surface and neural ectoderm before the migration of neural crest cells that separate the two layers that form the mesenchyme destined to be the bony orbit.7 Why these sequestrations become cystic and tend to form at suture lines is obscure.

The radiological features of our case are typical. In general, the expansile lesions appear cystic on skull roentgenograms and frequently involve the orbital and/or frontal bones. The surrounding bone may be sclerotic, and the cyst capsule may be calcified or contain bone fragments. Diploetic calvarial lesions may be dumbbell-shaped and cause displacement of the dura to the intracranial space and the periosteum to the orbit.2

Complete surgical removal is the therapy of choice. Recurrence, although rare, is either from incomplete removal or undetected multiple cysts.

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Picture of the Month

Carine Stromquist, MD, George P. Giacoia, MD (Contributors); Murray Feingold, MD (Section Editor)

Figure 1.

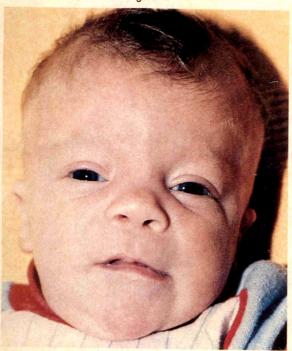


Figure 2.

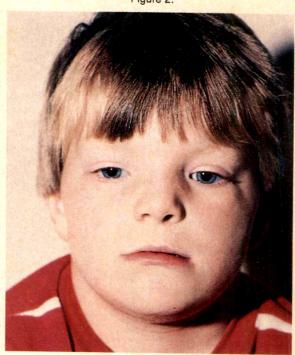
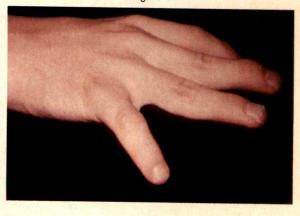


Figure 3.



Figure 4.



Accepted for publication Feb 12, 1988.
Contributed from Department of Pediatrics,
The University of Oklahoma, Tulsa.
Reprint requests to National Birth Defects
Center, Kennedy Memorial Hospital, 30 Warren
St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Figs 1 and 2.—Typical facial appearance with rounded facies, broad nasal bridge, upturned nose with anteverted nares, and long, broad philtrum.

Figs 3 and 4.—Unusual positioning of fingers, flexion contractures, and syndactyly.

Manifestations

Aarskog's syndrome is characterized by short stature and facial, digital, and genital anomalies. The facial features consist of a round facies, widow's peak, ocular hypertelorism, ptosis of the eyelids, downslanting palpebral fissures, short nose with anteverted nostrils, broad and long philtrum, and maxillary hypoplasia. There may be a delay in the eruption of the teeth, hypodontia, and malocclusion. Ventral scrotal folds (shawl scrotum), inguinal hernias, cryptorchidism, and normal sexual development are present. Skeletal abnormalities include unusual positioning of the fingers, syndactyly, foot deformities such as metatarsus varus and bulbous toes, pectus excavatum, and spinal anomalies. Final height is usually in the low-average to average range. Other less common findings include ophthalmoplegia, a protruding buttonlike umbilicus, congenital scalp and skull defects, and unusual cerebral venous drainage.

Intelligence is generally normal, although there are some reports of mild retardation and/or learning disabilities. With the exception of one report of isolated growth hormone deficiency, results of endocrine tests have been normal.

Genetics

Various types of genetic transmission have been reported but X-linked recessive is the most likely form of inheritance. Other reported modes of inheritance are X-linked semidominant and male-limited autosomal dominant. Carrier females may show mild symptoms, including short stature, widow's peak, ocular hypertelorism, and small hands. A recent report in-

dicated that the locus for Aarskog's syndrome was present on X q13.

Treatment

Genetic counseling should be provided. Orthopedic, orthodontic, and surgical (orchiopexy if cryptorchidism is present) treatment may be indicated.

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The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributors name. There is no charge for reproduction and printing of color illustrations.



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prostatic hypertrophy, and bladder neck obstruction Use with CNS Depressants: Tavist (clemastine fumarate) has additive effects with alcohol and other CNS depressants (hypertress sentatives tranquilizers etc.)

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Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation. Respiratory System: Thickening of bronchial secretions

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness. Cardiovascular System: Hypotension, headache, palpita-

Cardiovascular System: Hypotension, headache, palpita tions, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia agranulocytosis.

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Cyclosporine Therapy for Steroid-Resistant Nephrotic Syndrome

A Controlled Study

Eduardo H. Garin, MD; John K. Orak, MD; Karen L. Hiott, RN; Susan E. Sutherland, MS

 We have conducted a controlled trial on the efficacy of cyclosporine in eight patients with steroid-resistant nephrotic syndrome (four with idiopathic minimal lesion nephrotic syndrome and four with focal segmental glomerulosclerosis). Patients were randomly allocated to a cyclosporine (5 mg/kg/d) or a control group. After eight weeks of therapy and one month without cyclosporine therapy, patients in the control group were given cyclosporine for eight weeks and those in the cyclosporine group became controls. Before the initiation of treatment, there was no difference between the groups with regard to proteinuria and serum albumin levels. Proteinuria remained unchanged in the cyclosporine group, while there was a significant increase in proteinuria in the control group. There were no significant changes in serum albumin levels in either group during the trial. This study does not support the use of cyclosporine at the dose of 5 mg/kg/d in patients with steroid-resistant minimal lesion nephrotic syndrome or focal segmental glomerulosclerosis.

(AJDC 1988;142:985-988)

Circumstantial evidence suggests that idiopathic minimal lesion nephrotic syndrome (IMLNS) and focal segmental glomerulosclerosis (FSGS) are immunologically mediated diseases. 1.2 The current postulate is that lymphokines secreted by the T cell cause the increase in glomerular per-

meability to plasma proteins in these diseases.^{3,4}

Proteinuria remits in the majority of patients with IMLNS and in some of those with FSGS after corticosteroid therapy.⁵ The morbidity associated with chronic nephrotic syndrome is high for the patient who fails to respond to this mode of therapy.

Cyclosporine is a cyclic endecapeptide that acts on T cells and inhibits the production of lymphokines. ^{6,7} On the basis of this effect, cyclosporine has been administered to steroid-resistant patients with conflicting results. ⁸⁻¹³ The lack of a control group in all previous studies has made results difficult to interpret, since spontaneous remissions do occur in patients with IMLNS and FSGS. We conducted a controlled study on the efficacy of cyclosporine in steroid-resistant patients with IMLNS and FSGS.

PATIENTS AND METHODS

Six male and two female patients with idiopathic, steroid-resistant nephrotic syndrome were included in the study after written informed consent was obtained. Their ages ranged from 3 to 18 years, with a median age of 12 years. Four patients had IMLNS and four had FSGS, as defined by the International Study of Kidney Disease in Children. When entered in the study, all patients had creatinine clearances greater than 0.83 mL/s/1.73 m².

Steroid resistance was defined as massive proteinuria (>40 ${\rm mg/m^2/h}$, or >50 ${\rm mg/kg/d}$) and low serum albumin levels (<25 ${\rm g/L}$) after eight weeks of prednisone therapy at the dose of 2 ${\rm mg/kg/d}$ (up to 80 ${\rm mg/d}$). Prednisone therapy was discontinued for at least a week preceding the beginning of the study. Furthermore, prednisone was not administered to the patients during the trial.

The trial was a cross-over, randomized study. Patients were initially randomly allocated to either the cyclosporine group or the control group. Cyclosporine dosage for the treatment group was started at 5 mg/kg/d in one dose. Dosage was adjusted to keep the trough whole-blood level (measured by radioimmunoassay) at 200 ng/mL or less. Cyclosporine therapy was continued for a total of eight weeks. At the end of the eight weeks, and after a month without cyclosporine to allow any residual effect of the drug to wear off, patients initially allocated to the control group received cyclosporine as stated above and the patients initially in the cyclosporine group became controls.

Endogenous creatinine clearances and urinary protein excretion were measured in 24-hour urine collections. Protein excretion was expressed as milligrams of protein per milligrams of urinary creatinine. Serum creatinine, albumin, cholesterol, bilirubin, aspartate aminotransferase and alanine aminotransferase, lactic dehydrogenase, alkaline phosphatase, and complete blood cell counts were obtained at each clinic visit. All measurements were obtained weekly while patients were receiving cyclosporine therapy and every other week for patients in the control group. In addition, patients taking cyclosporine had a cyclosporine trough level measured at each weekly visit.

Statistical analyses were done using oneway analysis of variance for repeated measures. Due to the nature of the variables observed (urinary protein, albumin, and creatinine clearance), a log transformation was utilized. The data for these variables were analyzed in a univariate fashion using the repeated measures option in the SAS procedure GLM (General Linear Models).¹⁶ Whenever a significant difference was detected, Duncan's multiple range test was used to distinguish the mean differences between the observations within the same group.

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| Patient No./ Age, y (mo)/Sex | | | Pathologic Features and Duration of NS Before Renal Biopsy, mo |
|---------------------------------|--------|-----|---|
| 1/18(7)/M | 3 (11) | 176 | ML, 4; ML, 27; ML, 180 |
| 2/17(5)/M | 17 (0) | 5 | ML, 3 |
| 3/5(7)/M | 5 (4) | 3 | ML, 2; ML, 13 |
| 4/3(3)/M | 2 (8) | 7 | ML, 1; ML, 15 |
| 5/16(6)/M | 16 (0) | 6 | FGS, 1 |
| 6/16(3)/F | 15 (9) | 6 | FGS, 3 |
| 7/6(1)/M | 2 (1) | 47 | MPGN, 11; FGS, 40 |

NS indicates nephrotic syndrome; ML, minimal lesion; FGS, focal glomerulosclerosis; and MPGN, mesangial proliferative glomerulonephritis

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| Table 2.—Serial Urinary Protein Excretion Values During Cyclosporine Therapy and Control Periods (Mean ± SEM)* | | | | | | | |
|--|------------|-------------|------------|----------------|----------------|--|--|
| | Weeks | | | | | | |
| Group | 0 | 2 | 4 | 6 | 8 | | |
| Cyclosporine | 12.5 ± 2.1 | 11.8 ± 2.3 | 11.6 ± 2.0 | 10.9 ± 2.2 | 11.7±3.1† | | |
| Control | 11.9 ± 2.4 | 15.5 ± 3.9‡ | 15.1 ± 2.6 | 15.7 ± 3.7 | 17.3 ± 3.5 | | |

^{*}P = .0286 for cyclosporine vs control group over eight weeks. Urinary excretion values in milligrams of protein per milligrams of creatinine.

P=.70 for baseline vs eight weeks within cyclosporine group.

6 (0)

 $\pm P = .002$ for baseline vs two weeks within control group.

8/7(4)/F

| Table 3.— | Serial Creatinii (| ne Clearance \ Control Periods | /alues During ((Mean ± SEM | Cyclosporine Th)* | erapy and |
|--------------|-----------------------|-----------------------------------|--------------------------------|--------------------------|------------------------------|
| | | | Weeks | | |
| Group | 0 | 2 | 4 | 6 | 8 |
| Cyclosporine | 1.23 ± 0.23 | 1.42 ± 0.28 | 1.42 ± 0.25 | 1.58 ± 0.48 | 1.12 ± 0.23† |
| Control | 1.50 ± 0.30 | 1.13 ± 0.35 | 1.02 ± 0.20 | $0.87 \pm 0.18 \ddagger$ | $\boldsymbol{0.87 \pm 0.22}$ |

^{*}P = .2398 for cyclosporine vs control group over eight weeks. Serial creatinine clearance values measured in milliliters per second per 1.73 meters squared.

†P = .48 for baseline vs eight weeks within cyclosporine group.

‡P = .023 for baseline vs eight weeks within control group.

| Table 4.—Serial Serum Albumin Values During Cyclosporine Therapy and Control Periods (Mean ± SEM)* | | | | | | |
|--|--------|--------|--------|------|---------|--|
| | Weeks | | | | | |
| Group | 0 | 2 | 4 | 6 | 8 | |
| Cyclosporine | 20 ± 2 | 20 ± 3 | 25 ± 2 | 24±3 | 24±3† | |
| Control | 20±3 | 21 ± 2 | 19 ± 2 | 17±2 | 18 ± 3‡ | |

^{*}P = .0824 for cyclosporine vs control group over eight weeks. Serum albumin values measured in grams per liter.

tP = .27 for baseline vs eight weeks within control group.

RESULTS

Clinical and pathologic features of the patients are given in Table 1. Serial urinary protein excretion, serum albumin, and creatine clearances

are given in Tables 2 through 4, respectively.

FGS, 9

Before therapy began, no statistical difference was found between patients in the cyclosporine group and the control group with regard to urinary protein, serum albumin, and serum creatinine levels.

When the cyclosporine and control groups were compared over time, urinary protein levels (P = .0286) (Table 2) were significantly higher in the control group, while there were no significant changes in creatinine clearance (P=.2398) (Table 3) or in the serum albumin level (P = .0824) (Table 4) between the groups. However, when the changes in these indexes were analyzed within each group, proteinuria remained unchanged in the cyclosporine group (P = .70), while a significant increase in urinary protein excretion was observed in the control group (P = .002). The increase was seen after two weeks in the trial. Despite the increase in proteinuria in the control group, the serum albumin concentration did not change significantly (P = .27). No changes in serum albumin levels were observed in the cyclosporine group (P=.09). Finally, the administration of cyclosporine was not associated with a change in creatinine clearance (P = .48), while creatinine clearance decreased with time in the control group (P=.023). The change was observed six weeks into the study.

When individual responses were analyzed, no patient either in the IMLNS group or in the FSGS group had resolution of proteinuria and a normal serum albumin level during cyclosporine therapy.

No major side effects were observed during cyclosporine therapy. During the trial, no patient experienced hypertension in either the cyclosporine or control group. One patient receiving cyclosporine and two patients in the control group had a decrease of more than 20% of their creatinine clearances at the end of the trial. This decrease in clearances could not be attributed to hypovolemia, and these patients (all with FSGS) had subsequent further deterioration of their glomerular filtration rate. No changes in complete blood cell counts or liver enzyme levels were seen in either group of patients during the trial.

COMMENT

This study demonstrates that in patients with steroid-resistant nephrotic

[†]P = .09 for baseline vs eight weeks within cyclosporine group.

syndrome and IMLNS or FSGS, cyclosporine therapy seems to have a minor effect on proteinuria, since during its administration there was no further increase in urinary protein excretion. However, this finding did not have clinical significance because proteinuria remained within the nephrotic range and serum albumin below normal levels in all patients.

The increase in proteinuria during the follow-up of the control group has not been described previously. This is not likely due to a residual effect of cyclosporine, because no significant decrease in proteinuria was observed after cyclosporine therapy. However, if this residual effect occurs, it should balance out over the two groups by the randomization procedure. Perhaps the increase in proteinuria in the control group was the result of a further deterioration of the glomerular permeability, as we observed further reduction in glomerular filtration.

Although the number of patients included in the study may be thought to constitute a small sample, we believe that to continue to recruit additional patients was not warranted for the following reasons. The aim of the study was to assess the ability of cyclosporine to induce remission in certain type of patients with steroidresistant nephrotic syndrome. Normalization of the proteinuria was the goal of the cyclosporine therapy. Since the level of the protein-creatinine ratio before cyclosporine therapy was 10 or more and the normal protein-creatinine ratio is less than 1, a change of 10 or more units after cyclosporine therapy will be indicative of clinical efficacy. Statistical analysis of the data shows that only a small number of patients is needed to test the hypothesis. A pairwise difference in proteinuria of 10 or more units yields an approximate sample size of five patients, with an associated power of greater than 90% (β <.1). Thus, the probability of committing a type II error is rather low. Given the power of our statistical analysis, we decided not to enter any more patients in the protocol.

The permeability of the glomerular capillary wall to plasma proteins depends on the charge and size of the

protein and glomerular hemodynamic factors.16 Although cyclosporine is known to decrease the glomerular filtration rate.17 the mechanism for arresting the worsening of the proteinuria in our patients does not seem to be caused by hemodynamic factors because the creatinine clearance remained unchanged throughout cyclosporine therapy. It is postulated that depletion of the negative charge of the glomerular capillary wall may contribute to an increased glomerular permeability to plasma proteins by altering the selective properties of the matrix of the filtration barrier. It is thought that proteinuria in IMLNS and FSGS could be caused by lymphokines either by neutralizing the capillary wall negative charges or by changing the metabolism of the glomerular basement membrane compounds.18 Thus, stabilization of the proteinuria could be due to a partial inhibition of the pathogenic lymphokine by cyclosporine. Unfortunately, because the lymphokine has not been identified, the effect of cyclosporine on its secretion cannot be confirmed.

This study contrasts with those uncontrolled studies showing a high rate of complete remission of the nephrotic syndrome during cyclosporine therapy for steroid-resistant patients.8,12,13 It is unlikely that the difference is due to spontaneous remissions, since none was observed in our control group. Rather, the difference could be explained by the process of selecting the patients. A review of the literature suggests that cyclosporine efficacy is higher in patients who respond to prednisone therapy.9.11,12 A less stringent definition of steroid resistance (persistence of the nephrotic syndrome only after four weeks of prednisone therapy) would allow the inclusion of patients who could have still undergone remission taking prednisone, and could have a higher chance to respond to cyclosporine therapy. In some of the studies showing a high rate of remission of the nephrotic syndrome, the definition of steroid resistance is not given¹⁸ or the patients received the full dose of prednisone (2 mg/kg/d) for less than eight weeks. 12 Our results are comparable with those of Niaudet et al,11 who treated patients

for one month with prednisone (2 mg/kg/d) followed by three intravenous boluses of methylprednisolone without a response before considering them to be steroid resistant.

The efficacy and side effects (such as nephrotoxicity or hepatotoxicity) of cyclosporine seem to correlate with the trough blood levels of the drug. Published reports on cyclosporine and nephrotic syndrome can be compared because they all use the same method (radioimmunoassay). Niaudet et al, who kept plasma trough levels between 50 and 150 ng/mL, reported results similar to ours. In contrast. Meyrier et als described remission in four of the six patients treated. However, cyclosporine levels (plasma? whole blood?) were higher, ranging from 150 to 750 ng/mL, which suggest that an increase in dosage could be effective in inducing remission. Increasing the dosage, however, increases the risks of side effects, in-Moreover, cluding nephrotoxicity. because of uncertainty concerning possible irreversible toxicity of cyclosporine, the Food and Drug Administration requests that all investigators using the drug for indications other than organ transplant adjust the dosage so that trough whole-blood levels measured by radioimmunoassay be maintained at or below 200 ng/mL.

The length of therapy is another factor to be considered in assessing the efficacy of cyclosporine. It is unlikely that our failure to show an improvement in proteinuria could be due to an inappropriately short course of therapy, because in the previous studies, remission occurred within eight weeks of the onset of cyclosporine therapy.

In summary, our experience does not support the use of cyclosporine at the dose of 5 mg/kg/d in patients with steroid-resistant IMLNS or FSGS.

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Book Review

Pediatric Dermatology, edited by Lawrence A. Schachner and Ronald C. Hansen, 1641 pp, with illus, \$295, New York, Churchill Livingstone Inc, 1988

Pediatric dermatology is a subspecialty of dermatology that has, over the past decade, grown in influence and scope. The number of talented clinicians dedicated to the care of children with cutaneous disorders has also increased. This ambitious reference text is testament to that fact. It consists of individual chapters written by many of the leading authorities in pediatric dermatology, six of whom have written their own excellent, though less comprehensive, texts. The list of contributing authors is a virtual "who's who" of pediatric dermatology.

The text is more extensive and detailed than previous works. It covers everything from the everyday management of common skin conditions to the once-in-a-lifetime patient with a rare genodermatosis. Each chapter contains numerous current literature references. After the presentation of each disease entity there is a section on the pediatric concerns of the disease that discusses how the disease affects psychosocial development, growth, and other organ systems. The photographs throughout are excellent and numerous, including 140 color and 800 black-

and-white photographs.

As with other major dermatology texts, the book does not address basic morphological group diagnosis, for example, how to differentiate eczematous from papulosquamous processes. Dermatology reference texts assume that the reader already knows how to do this. This can be a problem for nondermatologists and is best solved by reading one of the books specifically devoted to this purpose (one of the best is Dermatology for the House Officer, by Peter J. Lynch, MD, Baltimore, Williams & Wilkins).

Topics of particular day-to-day interest to pediatricians abound, and a small sample follows. There is discussion of the psychosocial aspects of skin disorders and of sexually transmitted diseases and acquired immunodeficiency syndrome. Surgical techniques are covered, and there is excellent instruction with photographic illustration of the techniques and interpretation of fungal potassium hydroxide scrapings and scrapings for scabies. The clinical and laboratory differential of pustular disorders in the newborn is quite helpful. Management of congenital nevocellular nevi, vascular malformations, acne, and eczema is discussed. Vascular reaction patterns, including urticaria, erythema multiforme, Stevens-Johnson syndrome and the ever popular "maculopapular erythema" (a term not used by dermatologists), are discussed in a reasonable, clinically oriented framework. The chapter on viral diseases includes a very helpful table differentiating rubella, measles, erythema infectiosum, roseola, varicella, and enteroviral exanthems. The chapter on infestations contains interesting historical perspective and is quite humorous. There is an entire section devoted to injuries that includes venomous animal injuries as well as physical injuries due to child abuse.

This excellent comprehensive work will become the major pediatric dermatology reference text. The book is clinically practical and serves as an all-inclusive reference text. It will seem relatively expensive to pediatricians; this is chiefly due to the length of the book (over 1600 pages) and the numerous photographs; however, it is very similar in price to other dermatology reference texts. Thirty percent of all visits to a pediatrician involve a primary or secondary cutaneous complaint. Pediatricians need a comprehensive, well-illustrated, well-referenced, logically organized reference text, and this book fits the bill. It belongs in the library of all academic institutions and in the offices of all clinicians who care for children with cutaneous disorders.

ELAINE REMMERS, MD Department of Dermatology 3288 Moanalua Rd Honolulu, HI 96819

Magnetic Resonance Imaging in the Assessment of Medullary Compression in Achondroplasia

Ioan T. Thomas, MB, BCh; Jaime L. Frias, MD; Jon L. Williams, MD; William A. Friedman, MD

 Children with achondroplasia may be at increased risk of developing apneic episodes and of dying unexpectedly. The risks seem to be related to neural axis compression by an abnormal cranial base and may be complicated by the development of hydrocephalus. We used magnetic resonance imaging to study five children with achondroplasia. All of them demonstrated a discrepancy between the size of the brain stem and the foramen magnum. Comprehensive prospective assessment of infants with achondroplasia, including the use of new imaging techniques, will provide important information concerning the natural history of the relationship of the neural axis to the bony posterior fossa and upper cervical spine in this condition. It may also help to identify those patients at risk before the development of life-threatening medullary compres-

(AJDC 1988:142:989-992)

Achondroplasia, one of the most common chondrodysplasias, is associated with a number of incapacitating and sometimes fatal neurologic complications.1-6 In childhood the major impact has probably not been fully appreciated, but recent reports have suggested an increased incidence of apneic episodes and sudden infant death related to cervicomedullary compression, often occurring in children who were believed to have no major neurologic problems. 6-9

The demographic pattern of infant

death in achondroplasia has certain superficial similarities to that seen in the sudden infant death syndrome, and in eight of 11 recently reported cases death was attributed to that cause.7 The patients were infants between 2 and 5 months of age and all were considered healthy without overt neurologic complications, with normal developmental milestones, and with heights and head circumferences within the normal range for children with achondroplasia. Deaths were different from those usually seen in sudden infant death syndrome as four of 11 children died during the day, three of them while asleep in unsupported sitting positions.7 In view of this experience, we decided to evaluate the relationship of the neural axis to the posterior fossa and upper cervical spine in a small number of children with achondroplasia by using magnetic resonance imaging (MRI). 10 This technique offers certain advantages over computed tomographic (CT) scanning in that it employs nonionizing radiation, allows direct sagittal and coronal imaging, and requires no instillation of radiopaque contrast medium into the subarachnoid space. Moreover, MRI allows for excellent demonstration of posterior fossa structures because bone attenuation, a formidable problem with CT, does not occur with MRI.10

PATIENTS AND METHODS

Patient selection was based largely on the patients' ability to cooperate in the course of the investigation and not on neurologic status. Ages ranged from 18 months to 12 years. Two of the children had sleep apnea that was evident to the parents and was documented by sleep studies. Both children had normal somatosensory evoked potentials (SEPs). In one of them (18 months of age) the apnea was believed to

have features of both central and obstructive types, whereas in the other child (6 years old) the apnea was said to be obstructive. We defined central apnea as apnea associated with an absence of respiratory effort and obstructive apnea as respiratory effort against an obstructed airway. All of the children had head circumferences within the normal range for achondroplasia," but above the 95th percentile for normal children. All subjects showed some degree of hydrocephalus by CT scan or MRI assessment; two had ventriculoperitoneal shunts in place.

RESULTS

A summary of the clinical and MRI findings are seen in the Table. The MRI scan (Fig 1) demonstrated a tight foramen magnum in all five children. In four children there appeared to be compression of the neural axis at the level of the foramen magnum or the arch of C1, with kinking of the neural axis by the posterior margin of the foramen magnum in one child. In a fifth child there was also an anterior indentation of the pons by an abnormal clivus (Fig 1 and Table). Two children also had mild Arnold-Chiari malformations.

COMMENT

A number of recent reports have documented recurrent episodes of apnea, quadriparesis, and sudden infant death as complications of childhood achondroplasia. 2,6-9,12-14 The authors of these reports have emphasized the sudden and unexpected nature of these catastrophic complications, and at least one author commented on the fact that apnea may be the sole manifestation of medullary compression in children with achondroplasia.*

These major neurologic complications are better understood if one appreciates the developmental abnor-

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| Patient No./ Age/Sex | Apnea | Shunt | Hydrocephalus | Magnetic Resonance Image | | |
|-------------------------|-------|--------|---------------|---|--|--|
| 1/8 y/M | | Maries | + | Posterior compression of medulla by foramen magnum | | |
| 2/12 y/M | | + | + | Anterior indentation of pons; some compression at craniocervical junction | | |
| 3/10 y/M | After | + | + | Cord compressed by odontoid and arch of C1 | | |
| 4/6 y/F | + | | + | Cord compressed bilaterally by foramen magnum | | |
| 5/18 mo/M | + | war. | + | Tight foramen magnum | | |

^{*}Minus sign indicates absent; plus sign, present.

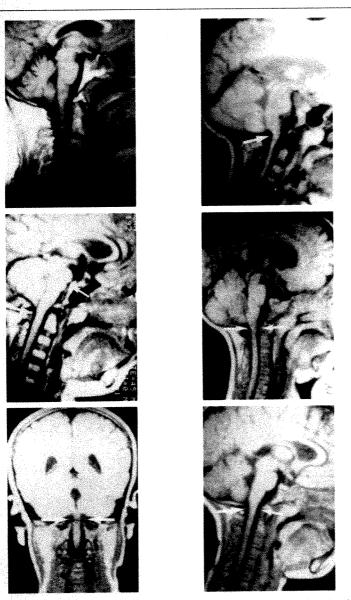


Fig 1.—Magnetic resonance imaging appearance in patients with achondroplasia. Top left, Normal. Top right, Posterior compression of medulla. Center left, Anterior indentation of pons, some compression at craniocervical junction. Center right, Posterior indentation of medulla. Bottom left, Bilateral compression of medulla. Bottom right, Tight foramen magnum.

malities of the skull that are seen in all children who have achondroplasia. The human skull is composed of three elements, the facial skeleton, the cranial vault, and the cranial base. The cranial base comprises the ethmoid, the sphenoid, the petrous portion of the temporal bone, and most of the occipital bone (Fig 2). The growth of these bones, except that of the planum occipitalis of the occipital bone, is affected in achondroplasia, since the bones develop by endochondral ossification. As a result, the foramen magnum, flanked by elements of the basiocciput, is markedly narrowed and triangular and has two bony lateral protuberances that represent enlarged articular surfaces between the lateral and basioccipital segments of the occipital bone. Similar excrescences, analogous to the epiphyseal enlargement seen in the long bones, are found between the lateral and planum nuchale segments. The planum nuchale, the basiocciput, and the lateral segments of the occipital bone form the floor and lateral walls of the posterior fossa and result in its being smaller in all its dimensions. The planum occipitalis grows by membranous ossification and is, therefore, normal.

The secondary changes are due to skeletal adaptation to the progressive expansion of the brain caused by hydrocephalus and are distinct from the primary changes caused by the chondrodysplastic process. The skull is dolichocephalic because of anterior rotation of the frontal bone and posterior rotation of the planum occipitalis of the occipital bone (Fig 2). In addition, the skull's large size is due to an increase in the size of the cranial vault. The size of the facial skeleton is normal, although the nasal choanae may be smaller because of the narrowness of the cranial base.13

We believe that the anomalies of the cranial base outlined above are the cause of the neurologic complications of hydrocephalus and cervicomedulary compression that are seen in children with achondroplasia.

There has been considerable debate concerning the pathogenesis and even the existence of the hydrocephalus associated with achondroplasia. 4.15.16 We suggest that there now exists ir-

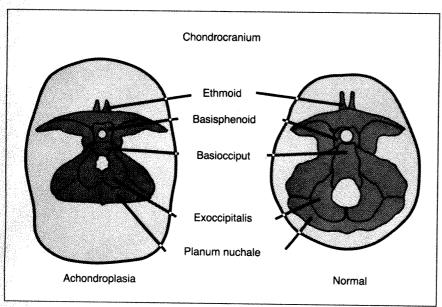


Fig 2.—Appearance of cranial base in a patient with achondroplasia (left) and in a normal patient (right).

refutable evidence that demonstrates that hydrocephalus is commonly associated with achondroplasia. 3.4,16-20 The degree of ventricular dilatation is variable and many children have arrested hydrocephalus that may not need a shunt.

The pathogenesis of the hydrocephalus is linked to the anatomic abnormalities in the occipital bone that produce intracranial venous hypertension. The cerebral venous circulation involves the return of blood from the cerebral veins to the sagittal sinus that then runs to join with the straight sinus at the torcular Herophili. Blood flows through the lateral or sigmoid sinuses to the jugular foramina, whence it leaves the skull and drains bilaterally into the internal jugular veins.

Venous obstruction at the jugular foramen has been demonstrated by one group of workers,²¹ while others have explored the relationship between ventricular pressures and the pressure within the sagittal sinus.²²⁻²⁵ These studies have demonstrated venous obstruction with elevated pressure in the sagittal sinus and dilatation of the subarachnoid cisterns. Our interpretation of these findings is as follows. The obstruction at the jugular foramen elevates the intracranial venous pressure and decreases absorption of cerebrospinal fluid (CSF) into

the sagittal sinus, thereby producing a communicating hydrocephalus. Some children with achondroplasia may develop noncommunicating hydrocephalus with more severe ventricular dilatation, possibly on the basis of obstruction of the fourth ventricular foramina.

In addition to hydrocephalus, unexplained apnea and sudden unexpected death in children with achondroplasia have recently been documented.7 Of 13 children, 11 died suddenly and unexpectedly and many showed evidence of acute and chronic compression of the medulla and cervical spinal cord. These compressive changes were sometimes severe and obvious, while in other cases external signs of damage were few or nonexistent; however, even in these cases histologic examination disclosed pyknosis of neural cell bodies, gliosis, and edema at the level of the foramen magnum.7

One series demonstrated that 10% of patients with achondroplasia had severe respiratory complications, including sleep apnea, substantial hypoxemia, and cor pulmonale. One of these children, who died at 3½ years of age, showed compression of the distal medulla and proximal spinal cord.

Another publication⁶ provides details of six cases presenting in infancy with respiratory symptoms and quad-

riparesis related to a small foramen magnum. These children were treated with foramen magnum decompression and demonstrated immediate postoperative improvement in their respiratory difficulty, with gradual disappearance of their limb paresis. Most patients had a moderate degree of hydrocephalus with dilatation of the cortical sulci and basal cisterns. The cortical veins were dilated, and anastomotic channels were well developed. The transverse sinuses and torculares Herophili were dilated and there was narrowing at the jugular foramina with prolonged circulation time. Two children showed a complete absence of drainage of CSF from the exit foramina of the fourth ventricle. In eight cases myelography demonstrated that the foramen magnum was encroached on by a bulbous odontoid process and the thickened posterior edge of the foramen magnum, both of which compressed the medulla. Radioisotope cisternography showed concentration of the isotope in the sagittal region that persisted for 72 hours and suggested considerable delay in CSF absorption into the sagittal sinus.

Medullary compression may exhibit few neurologic signs, and apnea may be its sole manifestation.8 It may be evaluated using SEP measurement. Patients with achondroplasia who have medullary compression may show, on SEP, increased latency and decreased amplitude above the cervical cord. 26 In this study of 23 patients with achondroplasia,26 seven symptomatic patients had abnormal SEPs, with the level of the abnormality correlating well with the patients' symptoms. In the control group of 16 asymptomatic patients with achondroplasia, seven had abnormal SEPs with a pattern suggesting cervicomedullary localization, two demonstrated foramen magnum stenosis on further investigation, and one patient, a 6-month-old girl, showed no SEP response above the medulla. This patient proved to have obstructive hydrocephalus that was treated by surgical decompression of the foramen magnum and CSF shunting. Five months later the patient's SEP responses had returned to normal and her CT findings were improved.

Recently, a comprehensive evaluation of 26 children 4 months to 6 years of age with achondroplasia was reported.27 The foramen magnum was small in 25 of 26 patients as assessed by a reconstructed midline sagittal CT scan and 11 patients demonstrated spinal cord atrophy. Bony anomalies of the posterior fossa included a forward extension of the squamous portion of the occipital bone, a thickened posterior rim of the foramen magnum. and dysplasia of the odontoid process.

The SEPs were abnormal in nine patients who were believed to have cervicomedullary compression, and all nine had respiratory problems and were subjected to neurosurgical decompression. At operation, all of these patients had severe cord compression with atrophy. The results of surgery demonstrated marked improvement in five patients with one fatality three weeks postoperatively.

Most children with achondroplasia do not suffer from disabling neurologic problems but some of them may be in a precarious balance because of the double jeopardy of cervicomedullary compression and hydrocephalus. It is difficult to predict which children will develop life-threatening complications. We, therefore, need to assess such children prospectively using modern, sophisticated, noninvasive techniques to learn more of the natural history of the relationship of the neural axis to the posterior fossa and upper cervical spine.28,29

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In Other AMA Journals

ARCHIVES OF DERMATOLOGY

Hereditary Progressive Mucinous Histiocytosis in Women: Report of Three Members in Family

Konrad Bork, MD, Nikolaus Hoede, MD (Arch Dermatol 1988;124:1225-1229)

Serum Concentrations of Growth Hormone, Insulin, Free Thyroxine, Thyrotropin, and Cortisol in Very-Low-Birth-Weight Infants Receiving Total Parenteral Nutrition

Keith S. Kanarek, MD, MPH; Carmen Villaveces, MD; G. Duckett; Allen Root, MD

 Serum concentrations of growth hormone, insulin, free thyroxine, thyrotropin, cortisol, and glucose were measured during four time periods (0 to 4, 5 to 11, 12 to 18, and ≥19 days of life) in 16 mechanically ventilated very-low-birthweight infants (mean [±SD] gestational age, 29 ± 1.4 weeks; mean [±SD] birth weight, 1017 ± 196 g) receiving total parenteral nutrition and in 21 very-lowbirth-weight infants not requiring mechanical ventilator support (mean [\pm SD] gestational age, 30 \pm 1.7 weeks; mean [±SD] birth weight, 1149 ± 210 g) fed enterally. There were no significant differences in the serum concentrations of the hormones or in the glucose levels between the two groups at any time interval. Present data demonstrate no significant difference in the serum concentration of glucose, insulin, growth hormone, cortisol, free thyroxine, and thyrotropin between very-low-birthweight infants fed enterally and those maintained on a regimen of total parenteral nutrition.

(AJDC 1988;142:993-995)

Advances in the respiratory and nutritional management of the verylow-birth-weight (VLBW) infant (birth weight, <1500 g) have resulted in decreased mortality and morbidity. Although the vigorous VLBW infant may be fed enterally, parenteral feeding of the ill VLBW infant is frequently necessary. The endocrine milieu is important for the growth and development of the newborn, but this has not been thoroughly investigated

in VLBW infants who are receiving total parenteral nutrition (TPN). The purpose of this study was to compare the concentrations of growth hormone (GH), insulin, thyrotropin (TSH), free thyroxine (free T₄), and cortisol in VLBW infants receiving TPN with those in infants of similar weight and gestational age fed enterally. These hormones were chosen because they can be measured using standard radioimmunoassay methods, require small amounts of blood, have modifying effects on energy metabolism, and influence the feast-fast cycle.1

PATIENTS AND METHODS

All newborns with a birth weight of less than 1500 g and a gestational age of less than 32 weeks admitted to the Tampa (Fla) General Hospital neonatal intensive care unit between January 1986 and January 1987 were eligible for the study. Gestational age was estimated from maternal dates and ultrasonographic measurements and, when this information was not available, by physical examination of the newborn.2 Neonates were excluded or removed from the study if feeds were discontinued because of threat of necrotizing enterocolitis, or if the TPN was discontinued because of surgery, electrolyte imbalance, or metabolic imbalance (eg, persistent hyperglycemia, hypertriglyceridemia).

Initially all neonates received an intravenous infusion of dextrose-water (2.5 to 7.5 g/kg/d of dextrose, 80 to 100 mL/kg/d of water). Electrolytes (sodium, potassium, chloride, and calcium) were added to the infusion when urine output was established, usually by the second day of life. Fluid requirements were adjusted to maintain adequate hydration. On day 3 or 4 of life, 16 newborns who were unable to tolerate enteral nutrition because of severe respiratory distress requiring mechanical

ventilation began TPN. The amino acid concentration of TPN was increased daily in 0.5-g increments from 0.5 g/kg/d on the first day to a maximum of 3 g/kg/d. Lipid emulsion was similarly increased daily in 0.5-g increments from 0.5 g/kg/d on the day after the initiation of amino acids to a maximum of 2.5 g/kg/d. The TPN dextrosewater concentration was increased as tolerated (blood glucose levels maintained at <6.7 mmol/L) until 293 to 418 nonprotein kJ/kg/d were infused. All neonates were receiving at least 2.5 g/kg/d of amino acids and 2.0 g/kg/d of lipid emulsion by day 10 of life.

Twenty-one neonates able to tolerate enteral feeds by the fourth day of life were fed 54.4 kJ/oz of infant formula at 12 to 24 mL/kg/d, initially by continuous nasogastric infusion. The volume and concentration of formula were increased as tolerated until the administration of 418 to 502 kJ/kg/d was achieved. The newborns' feeds were advanced to three hourly bolus feeds in the third time period.

Serum samples for measurement of GH,3 insulin,4 free T4, TSH (free T4 [radioactively labeled with cobalt 57]/TSH [radioactively labeled with iodine I 125], Simultrac Radioimmunoassay-Immunodiagnostics, Becton Dickinson, Orangeburg, NJ), and cortisol (Coat-A-Count Cortisol-Diagnostic Products Corporation, Los Angeles) were obtained by venipuncture before the initiation of TPN or formula feeds and weekly thereafter. All samples from the same newborn were determined in one assay. The interassay coefficients of variation were less than 10% for all assays. Blood samples were drawn between 8:30 AM and 12 PM. In neonates receiving bolus feeds, samples were drawn one to two hours after the feed. Neonates were evaluated for patent ductus arteriosus by auscultation, conditions were confirmed with M-mode echocardiography, and they were examined for intracranial hemorrhage by ultrasound

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within two days of birth and weekly thereafter if clinically indicated. Weight was recorded daily utilizing a digital scale.

The investigation was approved by the Institutional Review Board, University of South Florida, Tampa. Parental permission was obtained for the studies.

Statistical analysis was by the two-tailed Student t test for paired data, χ^2 test, and one-way analysis of variance. A P value of .05 or less was considered statistically significant. All values were expressed as the mean \pm SD.

RESULTS

The clinical characteristics of the newborns are shown in Table 1. There

were no significant differences between the two groups in mean birth weights (1017 ± 196 g for the TPN group vs 1149 ± 210 g for the enterally fed neonates) or gestational age (29 ± 1.4 weeks for the TPN group vs 30 ± 1.7 weeks for the enterally fed neonates). The neonates in the TPN group required ventilatory support (by selection) and had a significantly higher incidence of patent ductus arteriosus and intraventricular hemorrhage. The TPN group gained less weight than did the enterally fed group. There was no neonatal mortality in either group.

Laboratory data are presented in Table 2. There were no significant differences in serum concentrations of insulin, GH, TSH, free T4, and cortisol between the enterally and parenterally fed neonates at any time. In both groups, serum levels of GH, cortisol, and glucose decreased, insulin levels increased, and free T4 and TSH values did not change over time. These changes were not statistically significant. The serum glucose level was slightly but not significantly increased in the TPN group, reflecting the high glucose concentrations in TPN fluids. There was no correlation between serum insulin and glucose concentrations nor between weight gain and serum levels of GH, insulin, free T4, or TSH.

COMMENT

There is little information concerning the endocrine status of low-birthweight infants receiving TPN. Although the mean birth weights and gestational ages were not significantly different between the two groups, the incidences of intraventricular hemorrhage and of patent ductus arteriosus were significantly higher in the TPN group. The average weight gain was less in the TPN group and reflected

| | TPN (n = 16) | EF (n = 21) | P Value |
|--|-----------------|--------------------------------|---------|
| Birth weight, g (mean ± SD) | 1017 ± 196 | 1149 ± 210 | NS |
| Gestational age, wk (mean ± SD) | 29 ± 1.4 | $\textbf{30} \pm \textbf{1.7}$ | NS |
| Ventilator, >3 d | 16 | 0 | .001‡ |
| Patent ductus arteriosus | 7 | 2 | .001‡ |
| Intraventricular hemorrhage | 8 | 1 | .001‡ |
| Average weight gain, g (mean ± SD) 5-11 d | -7.7 ± 69.5 | -29.9 ± 71 | NS |
| 12-18 d | 43.8 ± 63.5 | 125.8 ± 48.1 | .002§ |
| 19-26 d | 46.3 ± 80.7 | 148.5 ± 64.7 | .007§ |

^{*}TPN indicates total parenteral nutrition; EF, enterally fed

[§]Student's t test (P<.05).

| Table 2.—Serum Concentrations of Glucose, Insulin, GH, Cortisol, Free T ₄ , and TSH in Neonates Receiving TPN or EF* | | | | |
|---|-------------------------|-----------------------------|---------------------------|-----------------------|
| ų a | Days of Life† | | | |
| | 0-4‡ | 5-11 | 12-18 | 19+ |
| Glucose, mmol/L TPN | 6.6 ± 3.2 (2.7-14.5) | 6.2 ± 1.2 (3.8-8.3) | 5.3 ± 1.6 (2.7-8.5) | 5.2 ± 1.5 (3.3-7.2) |
| EF | 5.1 ± 1.9 (2.4-8.2) | $5.2 \pm 1.0 \ (4.0 - 6.9)$ | $5.7 \pm 1.9 \ (3.0-9.6)$ | 5.2 ± 0.9 (3.2-6.2) |
| Insulin, pmol/L TPN | 63 ± 50 (9-186) | 68 ± 52 (22-270) | 73 ± 106 (22-428) | 53 ± 105 (12-553) |
| EF | 42 ± 32 (21-138) | 51 ± 42 (22-178) | 73 ± 60 (15-177) | 49 ± 41 (15-179) |
| GH, μg/L TPN | 40.3 ± 16.0 (5.5-68.0) | 25.3 ± 13.2 (6.8-50.1) | 27.3 ± 18.0 (1.2-56.7) | 29 ± 19.4 (2.8-66.8) |
| EF | 41.4 ± 13.1 (20.6-71.1) | 23.8 ± 14.4 (2.0-47.5) | 27.5 ± 15.0 (9.9-50.0) | 18.0 ± 7.2 (5.1-31.8) |
| Cortisol, nmol/L TPN | 400 ± 280 (90-1040) | 200 ± 110 (70-390) | 170±120 (40-520) | 190±110 (30-440) |
| EF | 230 ± 130 (70-450) | $240 \pm 140 (50-470)$ | 170 ± 130 (30-460) | 160 ± 160 (10-700) |
| Free T ₄ , pmol/L TPN | 51 ± 42 (4-136) | 27 ± 26 (4-76) | 32±39 (4-126) | 48 ± 55 (4-206) |
| EF | 28 ± 32 (1-103) | 27 ± 36 (3-103) | 42 ± 53 (5-158) | 28 ± 48 (5-208) |
| TSH, mU/L TPN | 3.4±2.8 (0.6-9.0) | 5.0 ± 2.7 (0.4-10.6) | 3.4 ± 2.0 (1.5-8.8) | 4.4 ± 3.0 (1.5-15.9) |
| ef | 3.3 ± 3.3 (0.1-10.0) | 3.3 ± 3.5 (0.1-12) | 3.1 ± 1.4 (1.0-4.9) | 3.2 ± 2.3 (0.5-11.6) |

^{*}GH indicates growth hormone; T4, thyroxine; TSH, thyrotropin; TPN, total parenteral nutrition; and EF, enterally fed.

[†]Any value greater than .05 was considered to be not significant (NS).

[‡]x2 (P<.05)

[†]Values are mean ± SD, with range in parentheses.

Prior to TPN or EF.

both the smaller energy intake they received and the severity of illness compared with the enterally fed newborns. Nevertheless, present data demonstrate no significant differences in the serum concentrations of glucose, insulin, GH, cortisol, free T₄, and TSH between VLBW infants fed enterally and those maintained on a regimen of TPN. Our data are consistent with previously reported values for these hormones in studies performed on enterally fed neonates. ⁵⁻¹⁴

Although the enteroinsular axis is functional in newborns soon after birth, the insulin secretory response to glucose may not be fully developed until 110 days after birth, regardless of the route of administration of glucose. Bolus feeding of the premature newborn results in cyclical increments and decrements in serum glucose and insulin values,6 changes not seen in the newborn receiving continuous enteral feeds. 7.8 In premature newborns, insulin secretion in response to hyperglycemia is sluggish when compared with term newborns,5,9 while addition of amino acids is associated with enhanced secretion of insulin. 10-12 In our study, in both groups, serum insulin values increased over the first three weeks, suggesting enhanced secretion of insulin as a result of the functional maturity of the enteroinsular axis and the addition of amino acids or proteins to the diets. There were no significant differences between the TPN and enterally fed groups in free T4 levels; this was consistent with what was reported for premature infants. 12

Serum concentrations of GH were high and declined over several weeks in both groups of neonates, findings previously reported in normally fed term and preterm neonates. 14,15 The wide variations in serum concentrations of GH may be the result of pulsatile secretion and of stressful stimuli that may be triggered by changes in body temperature, changes in circulatory status, the stress of venipuncture, and the variable degree of illness. There was no correlation between serum concentrations of GH and rate of weight gain in either group.

The fetal adrenal cortex is functionally well developed by 28 weeks' gestation. Serum cortisol levels are elevated at birth and then decrease during the first ten days of life. 17,18 The individual values fluctuate and may be the result of behavioral states preceding blood sampling and the degree of illness.17 Our data are consistent with these findings and, in addition, demonstrate that there is no difference between newborns receiving TPN or fed enterally. In our study, the serum concentrations of GH, insulin, free T4, TSH, and cortisol were not influenced by TPN and were similar to those of premature neonates receiving enteral

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Quotables:

Notes on the Composition of Scientific Papers: Force, lucidity, unity, simplicity, economy of expression are virtues which we may all obtain: Originality will be as God pleases.

SIR T. CLIFFORD ALLBUTT Perspectives in Biology and Medicine 1985

Chlamydia trachomatis Fitz-Hugh-Curtis Syndrome Without Salpingitis in Female Adolescents

Debra K. Katzman, MD; Ira M. Friedman, MD; Catherine A. McDonald, MD, MPH; Iris F. Litt, MD

• We encountered seven female adolescents with the Fitz-Hugh-Curtis syndrome and no signs or symptoms of salpingitis. Six of the patients had cervical cultures positive for Chlamydia trachomatis. The Fitz-Hugh-Curtis syndrome should be included in the differential diagnosis of right-sided abdominal pain in the sexually active female adolescent to avoid unnecessary diagnostic procedures and to reduce the prevalence of chlamydial infection and its complications.

(AJDC 1988;142:996-998)

Perihepatitis is a localized inflammation affecting the upper anterior surface of the liver and the adjacent parietal peritoneum, resulting in fibrinous adhesions between the liver and the diaphragm.1 The syndrome, first described in 1919 by Stajano,2 is characterized by the acute onset of severe right upper quadrant abdominal pain resembling that of acute cholecystitis. In 1930 Curtis,1 and four years later, Fitz-Hugh,3 related the syndrome to gonococcal salpingitis. In recent years it has become clear that Neisseria gonorrhoeae is only one of several causative agents in the Fitz-Hugh-Curtis (FHC) syndrome, the most common of which is Chlamydia trachomatis. Studies in which both organisms were sought have strongly suggested that C trachomatis is far

more often the cause. ** It frequently occurs in young, sexually active females with acute pelvic inflammatory disease. Herein we describe seven sexually active female adolescents who presented with the FHC syndrome and had no clinical signs or symptoms of salpingitis, six of whom had a positive endocervical culture for *C trachomatis*.

The following patient reports underscore the importance of considering the FHC syndrome in the evaluation of the sexually active female adolescent with right-sided abdominal pain, even in the absence of salpingitis.

PATIENT REPORTS

PATIENT 1.—A 16-year-old nulliparous female adolescent presented to the primary care clinic complaining of right upper quadrant abdominal pain and persistent irregular vaginal bleeding of four weeks' duration. The pain was sharp and constant. It felt somewhat better in the sitting position and was aggravated by deep inspiration. Her last normal menstrual period occurred two months before her presentation, and she denied a vaginal discharge. She was sexually active and reported using condoms for contraception. Her gynecologic history was significant for gonococcal cervicitis several years ago, which was treated with "an antibiotic" on an outpatient basis.

The only abnormality found on physical examination was right upper quadrant tenderness. There was no guarding or rebound tenderness elicited on abdominal examination. The patient had a Sexual Maturity Rating (SMR) of V. The pelvic examination revealed minimal bleeding from the cervical canal. The cervix was not tender to manipulation, the uterus was not enlarged, and there were no adnexal masses. Results of the rectal examination were normal.

The initial laboratory results included a white blood cell (WBC) count of 12.1×10^{9} /L, with 0.76 neutrophils, 0.03 band cells, 0.16 lymphocytes, and 0.03 monocytes. The

erythrocyte sedimentation rate (ESR), as measured by the Westergren method, was 45 mm/h. Liver function tests, which included serum alanine aminotransferase and serum aspartate aminotransferase measures, yielded normal results. A serum pregnancy test was negative. An endocervical culture for N gonorrhea, a wet mount for Trichomonas vaginalis, and a potassium hydroxide preparation for yeast were negative. A kidney and upper bladder examination and an ultrasound examination of the abdomen and the pelvis revealed no abnormalities. On the fourth hospital day, the endocervical culture for C trachomatis was reported to be positive.

The patient was treated with doxycycline hyclate (100 mg orally every 12 hours). She was discharged on the fifth hospital day to complete a 14-day course of therapy. One month after her hospital admission, a repeated endocervical culture for *C trachomatis* was negative.

PATIENT 2.—A 16-year-old nulliparous female adolescent presented to the emergency room with a three-day history of right-sided abdominal pain. The pain was sharp and increased with deep inspiration, sitting up, and walking. The patient denied nausea, vomiting, diarrhea, dysuria, or vaginal discharge. Her last menstrual period had begun three days before presentation. The patient was sexually active and used condoms. The gynecologic history included an episode of N gonorrhea cervicitis the year before, which was treated with one dose of ampicillin trihydrate (3.5 g) and probenecid (1 g) orally. The patient's partner was also treated at that time. The patient was unavailable for follow-up.

The physical examination revealed a tearful young woman in moderate distress with normal vital signs. There was marked tenderness to deep palpation of the right upper quadrant. The pelvic examination disclosed a normal-appearing cervix and no abnormal vaginal discharge. There was no cervical motion or adnexal tenderness elicited on bimanual examination, nor were any masses palpated.

The laboratory results included a WBC

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Summary of History, Physical Examination, Laboratory Results, and Isolation in Patients With Fitz-Hugh-Curtis Syndrome*

| | History | Examination | | Laboratory Results | | | | Isola | ition |
|--------|---|-----------------|----------------------|--------------------|------------------------|-------------|-------------|--------------------------|---------------------------|
| Age, y | CC | Temperature, °C | Abdomen | ESR, mm/h | WBC, ×10°/L (P/Bds) | AST, U/L | ALT, U/L | Neisseria gonorrhoese | Chlamydia trachomatis† |
| 14 | RUQ pain | 38.2 | RUQ tenderness | 54 | 11.7 0.72/0.06 | 44 | 27 | ••• | + |
| 15 | RUQ pain, R shoulder pain | 37.0 | RUQ tenderness | 33 | 14.5 0.86/0 | 24 | 1 | + | 1 |
| 15 | R chest and shoulder pain | 37.4 | RUQ tenderness | • • • | * * * | 29 | 7 | within. | + |
| 17 | R-sided pain and SOB | 36.8 | RUQ tenderness | 53 | 6.9 0.76/0.01 | 42 | 15 | | + |
| 16 | RUQ pain, irregular vaginal bleeding | 36.3 | RUQ tenderness | 45 | 10.8 0.76/0.03 | 14 | 8 | None- | + . |
| 15 | R-sided flank pain | 37.2 | Right CVA tenderness | 33 | 10.4 0.64/0.10 | 22 | 13 | | + |
| 16 | RUQ pain | 37.6 | RUQ tenderness | 14 | 10.5 0.75/0.05 | 14 | 11 | **** | |

^{*}CC indicates chief complaint; P/Bds, polymorphonuclear cells/band cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; RUQ, right upper quadrant; plus sign, positive; minus sign, negative; SOB, shortness of breath; CVA, costovertebral angle. Adnexal tenderness, masses, and/or cervical motion tenderness were not found on examination in any of the patients.

†Complement fixation for C trachomatis was positive at 1:2048.

count of 10.5×10°/L, with a differential count of 0.74 neutrophils, 0.05 band cells, 0.17 lymphocytes, 0.01 monocytes, and 0.03 eosinophils. The ESR, as measured by the Westergren method, was 14 mm/h. The serum aminotransferase and serum aspartate aminotransferase levels were normal. Examination of the urine yielded rare trichomonads, and the endocervical culture for N gonorrhoeae was negative. One day later, the endocervical culture for C trachomatis was reported to be positive. The patient was given prescriptions for metronidazole (250 mg every eight hours for seven days) and doxycycline hyclate (100 mg every 12 hours for 14 days). The patient was unavailable for follow-up.

RESULTS

The patients ranged in age from 14 to 17 years (Table). None reported a history of significant lower abdominal pain before their presentation. Six experienced right upper quadrant tenderness on physical examination; none experienced cervical motion or adnexal tenderness on bimanual examination by experienced clinicians. Chlamydia trachomatis was isolated from the cervical canal in six of the seven patients. One patient had both C trachomatis and N gonorrhoeae isolated from the cervical canal. The one patient whose cervical culture was negative for C trachomatis, as well as for N gonorrhoeae and aerobic and anaerobic bacteria, had been treated with amoxicillin trihydrate for the

presumptive diagnosis of a urinary tract infection for ten days before her presentation. This patient underwent a laparoscopy that revealed "numerous filmy hepatic adhesions encasing bilateral tubes and ovaries with the adnexa adherent to the broad ligament . . . and adhesions from the anterior abdominal wall to the right lobe of the liver." Culture specimens for C trachomatis were taken during the laparoscopy and were reported to be negative. Serum complement fixation revealed a Chlamydia complement fixation antibody titer of 1:2048, consistent with a recent chlamydial infection. Serologic testing was not performed on any other patients.

The results of the laboratory tests for all seven patients are shown in the Table. The ESR was elevated in five patients, and the liver enzyme analysis results were normal in five of the patients. The WBC count was greater than $10.0 \times 10^9/L$ in five of the six patients in whom it was obtained, and a left shift was observed in all six cases.

COMMENT

The most common complaint in the patients described in this study was right upper quadrant pain or right-sided chest pain. The classic presenting symptom of perihepatitis, as defined in the literature, is "se-

vere pleuritic right upper abdominal pain."10 The pain can often radiate to the right shoulder, as seen in two of our seven patients. A friction rub may be heard during respiration. 10 According to Eschenbach and Holmes," concurrent left upper quadrant tenderness is not an uncommon finding. Left upper quadrant pain shifting to the right, with typical FHC symptoms as the primary presentation, has also been described. 12 Eschenbach 13 found that 60% of female adults with FHC syndrome have the onset of upper abdominal pain occurring at the same time as lower abdominal pain caused by salpingitis. However, 30% of adult patients have onset of pain three to 13 days after lower abdominal pain, and the remainder have onset of pain three to six days before lower abdominal pain.18 In the seven adolescent cases presented, none of the patients reported a history of lower abdominal pain before presentation. Lower abdominal tenderness and evidence of acute or subacute salpingitis was absent in all patients in this study.

Chlamydia perihepatitis has been described to occur in approximately 5% to 25% of salpingitis cases. 14-18 Mueller-Schoop et al,4 via laparoscopy, showed typical findings of the FHC syndrome in three women whose age, sexual activity, and symptoms suggested that a genital tract infection

may have spread to the peritoneum. Chlamydia cultures were not performed in that study. The C trachomatis FHC syndrome appears to be more common than is generally recognized.

The ascending spread of chlamydia, as with the gonococcus, in the female genital tract is postulated to occur cannalicularily, ie, through the cervical channel, the endometrial cavity, and the fallopian tubes into the peritoneal cavity and to the surface of intra-abdominal organs, such as the liver. 19 A report of gonococcal perihepatitis in a man with genital gonorrhea suggests, in addition, the possibility of spread by other mechanisms.20 If the assumption that our patients had genitally acquired infections is correct, then it appears that the infectious agent ascended from the cervical canal, reaching the liver capsule, without causing clinical signs and symptoms of salpingitis.

The laboratory tests revealed that the majority of our patients had normal liver function test results; this has been reported in other patients with FHC syndrome.21 It has been postulated that findings such as these indicate that chlamydia perihepatitis does not affect the liver parenchyma in contrast with perihepatitis caused by N gonorrhoeae. 22 This is supported by biopsy reports of serologically diagnosed C trachomatis in perihepatitis.21 Others have postulated that there may be a transient elevation of liver enzyme levels. The ESR was elevated in the majority of our patients as well, and this has also been observed in other cases. 10

To our knowledge, this is the first report of chlamydial perihepatitis without salpingitis in adolescents. In the absence of any genital tract signs or symptoms, the clinical presentation of chlamydial perihepatitis may be misinterpretated as cholecystitis, cholelithiasis, hepatitis, pleuritis, subphrenic abscess, perforated peptic ulcer, pyelonephritis, nephrolithiasis, appendicitis, ectopic pregnancy, abdominal trauma, or pancreatitis. 10.28 If unnecessary diagnostic and surgical procedures are to be avoided, the FHC syndrome must be included in the differential diagnosis of right-sided abdominal pain in the sexually active female adolescent. Performance of an endocervical culture for C trachomatis will facilitate its diagnosis and prevent unnecessary laparotomy. Early diagnosis and appropriate antibiotic treatment should reduce the morbidity and spread of chlamydial infections.

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Quotables:

Children's Names: The names of the children are sometimes an excellent guide to the fantasies of their parents.

Thomas McKeown Perspectives in Biology and Medicine 1986

Age-Specific Characteristics of Brain Death in Children

James C. Fackler, MD; Juan C. Troncoso, MD; Frank R. Gioia, MD

 Clinical and neuropathologic characteristics of 45 children who met criteria for brain death were analyzed. Children between 2 months and 1 year of age were compared with children older than 1 year and children older than 5 years. The observation period to fulfill brain death criteria was not different between the age groups. Deep tendon and spinal reflexes were preserved significantly less frequently in children younger than 1 year old. Diabetes insip-Idus and the necessity of inotropic support were significantly more frequent in children older than 5 years. Fifty-eight percent (26/45) of patients had no cerebral perfusion pressure before death. However, 18% (8/45) of patients never had a cerebral perfusion pressure below 40 mm Hg. No relationships could be shown between the clinical or physiologic factors and neuropathologic findings. We found no support for using different brain-death criteria for children between 2 months and 1 year of age.

(AJDC 1988;142:999-1003)

The report of the Medical Consultants on the Diagnosis of Death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research wrote the following in 1981:

The brains of infants and young children have increased resistance to damage and may recover substantial functions even after exhibiting unresponsiveness on neurological examinations for longer periods than do adults. Physicians should be particularly cautious in applying neurologic criteria to determine death in children less than five years.¹

The age distinction became one step more complex when the most recent Task Force for the Determination of

Brain Death in Children chose a threetier approach with different braindeath criteria for children younger than 2 months, between 2 months and 1 year old, and older than 1 year.2 The primary distinctions recommended by the task force were longer observation of young children before declaration of brain death (48 hours for children 7 days to 2 months old and 24 hours for children between 2 months and 1 year old) and the necessity of two corroborating electroencephalograms (EEGs) or one EEG and a corroborating radionuclide cerebral blood flow study. The task force also recommended that children older than 1 year be observed for no less than 12 hours (unless corroborating tests support the clinical diagnosis). However, just as age 5 years was chosen arbitrarily for "caution" by the President's Commission, the three age tiers of the task force are equally arbitrary.3

We examined, therefore, the clinical and neuropathologic findings of 47 consecutive brain-dead children seen over a two-year period. Young children $(2 \, months \, to \, 1 \, year \, old)$ were compared with older children (1 to 5 years old and older than 5 years). Because the children were observed for various lengths of time before declaration of brain death, we compared the periods of observation between the age groups. While this study cannot be considered a direct validation of braindeath criteria because the children who met the brain-death criteria were not supported until irreversible cessation of cardiovascular function, no discrepancies or irregularities were encountered when applying braindeath criteria formulated from experiences with older children and adults to infants older than 2 months. 1.4

PATIENTS AND METHODS

Children admitted to the Pediatric Intensive Care Unit (PICU) of The Johns Hop-

kins Hospital, Baltimore, between July 1984 and June 1986 were subject to retrospective analysis. The PICU is a multidisciplinary unit for children of all age groups except newborns. Brain death was diagnosed by criteria similar to those of the President's Commission. Specifically, children were declared brain dead if they were in coma of known irreversible cause and if they also met the following criteria: (1) absence of hypothermia, hypotension, and drug intoxication; (2) cerebral unresponsiveness; (3) apnea with arterial carbon dioxide tension greater than 60 mm Hg (without a history of chronic lung disease); (4) absent brain-stem reflexes (pupillary, oculocephalic, corneal response, vestibuloocular, gag reflex, and cough reflex); and (5) no neurologic improvement following at least 12 hours of observation (six hours if an EEG showed electrocerebral silences or if absent cerebral blood flow was documented by either a radionuclide scan or four-vessel arteriography). The period of observation did not vary with the age of the patient. Documentation of the complete neurologic examination was made by either a pediatric neurologist or a pediatric neurosurgeon. Alternatively, in children who received therapeutic pentobarbital sodium for the management of increased intracranial pressure (ICP), the clinical impression of brain death was confirmed by the absence of cerebral blood flow documented with a radionuclide scan or four-vessel arteriography. No child was supported until cardiovascular collapse. Forty-seven children fulfilled these criteria. Two children were excluded from all but the analysis of age distribution. A 17-year-old was excluded for lack of complete data. A 3week-old was excluded because the child was the only patient younger than 2 months old.

The children were examined for pupillary reflexes and level of consciousness at least every two hours. Complete neurologic examinations were done at least every 12 hours. The observation period was defined as the period between the first neurologic examination consistent with brain death and the actual declaration of death. During the observation period, the patients were mechanically ventilated and every effort was made to maintain hemodynamic stabil-

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ity. Spinal reflexes were said to be preserved when there was either unilateral flexion withdrawal to stimulation of the sole of the foot or upper abdominal reflexes. 6.7 Deep tendon reflexes specifically refer to stretch reflexes at the knees and elbows. Thermal instability was defined as a rectal temperature less than 35°C or the need to use warming blankets to maintain a normal core temperature. Hyperglycemia was defined as at least two sequential serum glucose determinations greater than 13.8 mmol/L during the hospitalization. Diabetes insipidus (DI) was defined as urine specific gravity less than 1.010 with urine output in excess of 2 mL/kg/h in the absence of the following: (1) glycosuria (urine glucose concentration >0.25% as measured by urine dipstick); (2) diuretic therapy during the preceding six hours; and (3) positive fluid balance.8 Confirmation of neurogenic DI was made by a 50% or greater reduction in urine output following intravenous arginine vasopressin infusion.

Intracranial pressure monitoring, which was performed with either an intraventricular catheter or a subarachnoid bolt, was not performed in every child.⁹ Cerebral perfusion pressure (CPP) was defined as the mean systemic arterial pressure minus the mean ICP. Pressure transducers were referenced at the level of the right atrium.

Brain specimens, which had been fixed in formaldehyde solution for at least two weeks, were examined. Tissues were paraffin embedded for sectioning and stained with hematoxylin-eosin. Neuropathologic findings were subjectively ranked by one observer (J.C.T.) from mild (1+) to severe (3+) for cerebral edema, neuronal anoxic changes, pituitary necrosis, and global softening. Secondary vascular changes were defined as the presence of midline hemorrhages in the midbrain and rostral pons, or infarction in the distribution of the posterior cerebral arteries. 10

The children were grouped by age for data analysis as younger than 1 year and older than 2 months, older than 1 year and younger than 5 years, or older than 5 years. The Mann-Whitney U test was used to compare the periods of observation. Fisher's exact test was used for all other comparisons.

RESULTS

The Figure shows the age distribution of all the patients. The median age of the entire group was 5.3 years and ranged from 3 weeks old to 17 years old. Twenty-three children were younger than 5 years old. The median age of this group was 1.3 years. Twelve

children were younger than 1 year; only one child was younger than 2 months. There were 23 children older than 5 years. The median age of this group was 10.2 years. Again, the 3-week-old and the 17-year-old were excluded from further analysis.

The primary neurologic diagnoses are shown in Table 1. Anoxic encephalopathy accounted for eight (73%) of 11 deaths in children younger than 1 year. Five of the eight patients died of sudden infant death syndrome while one patient each strangled, drowned, or had a cardiac arrest. Six (55%) of the 11 children between 1 and 5 years old had anoxic encephalopathy. Three children drowned, two suffocated, and one had a cardiac arrest. Two children (18%) younger than 1 year had neurologic examinations consistent with brain death when they were admitted to the PICU. Three children (27%) between 1 year and 5 years old and seven children (22%) older than 5 years similarly had neurologic examination results consistent with brain death when they were admitted to the PICU.

Clinical observations are summarized in Table 2. The periods of observation to fulfill the brain-death criteria did not differ between the age groups. The lengthy observation periods were primarily for family grieving considerations, performance of corroborating tests, and individual physician preferences. Of the 11 children younger than 1 year old, four (36%) were observed from six to 24 hours, four (36%) were observed from 24 to 48 hours, and three (28%) were observed for longer than 48 hours. Combining the children older than 1 year, 11 children (33%) were observed from six to 24 hours, 13 children (38%) were observed from 24 to 48 hours, and ten children (29%) were observed for longer than 48 hours (range, 49 to 150 hours). Deep tendon or spinal reflexes were seen at the time of death in less than half of the children. The absence of these reflexes during the observation period in children younger than 1 year was significantly different from the older children. Also significant was the finding of fewer spinal reflexes in children younger than 5 years compared with children older than 5 years.

The majority of children had thermal instability and were hyperglycemic. Most children required sympathomimetic drug infusions for inotropic support; however, the children older than 5 years required this support significantly more frequently than children younger than 5 years.

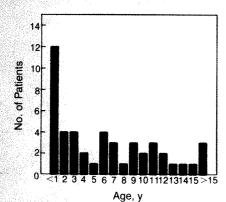
Corroborating blood flow studies confirmed absent cerebral circulation in 28 children: four children (36%) aged 2 months to 1 year, eight children (73%) aged 1 to 5 years, and 16 children (70%) older than 5 years had no cerebral blood flow. Electroencephalograms were obtained in all but four children. All 11 children beween 2 months and 1 year old showed electrocerebral silence. Ten of the 11 children between 1 and 5 years old showed electrocerebral silence; a single child in this age group did not have an EEG performed. Fourteen of the 20 EEGs obtained nearest the time of brain death in the 23 children older than 5 years showed electrocerebral silence.

Serum pentobarbital was detected at the time of death in one 2-year-old and in seven children older than 5 years. Absent cerebral blood flow was documented in each child. The median pentobarbital level was 36 μ g/dL and ranged from 18 to 171 μ g/dL. Excluding those children from the clinical data analysis did not change the statistical significance of any comparison.

Diabetes insipidus was completely absent in children younger than 5 years. Five patients (22%) in the oldest age group exhibited DI. Furthermore, three more patients (all aged 5 years or older) probably had DI, but confounding conditions (see "Patients and Methods" section) could not be excluded. This difference remained significant after exclusion of the children with detectable serum pentobarbital levels at death.

Intracranial pressure monitoring devices were used in seven patients (64%) younger than 1 year, in eight patients (73%) between 1 and 5 years old, and 18 patients (78%) of the oldest group. A CPP equal to zero was documented in three of the seven patients younger than 1 year and in 14 of the 18 oldest patients. However, one 9-month-old and three patients between 1 and 5 years old never had a

1000



Age distribution of brain-dead children.

| | 2-12 | | |
|-----------------------------|------|-------|-----------------|
| Diagnosis | mo | 1-5 y | >5 _} |
| Anoxic encephalopathy | 8 | 6 | 8 |
| Trauma | 2 | 2 | 8 |
| Meningitis | 0 | 0 | 1 |
| Cerebral abscesses | 0 | 0 | 1 |
| Acute hydrocephalus | 0 | 0 | 2 |
| Brain tumor | 0 | 0 | 1 |
| Hemolytic uremic syndrome | 0 | 1 | 0 |
| Hypertensive encephalopathy | 0 | 1 | 1 |
| Intracranial hemorrhage | 1 | 1 | 0 |
| Va sculitis | 0 | 0 | 1 |
| Total | 11 | 11 | 23 |

documented CPP below 40 mm Hg. Radionuclide cerebral perfusion scans were performed in three of these four patients, and all showed no cerebral blood flow. All four of these patients had EEGs documenting electrocerebral silence. Also, two of the patients older than 5 years never had a documented CPP below 40 mm Hg. One child had both a radionuclide cerebral perfusion scan documenting absent cerebral blood flow and an EEG documenting electrocerebral silence. The other child was declared dead solely on the basis of the neurologic examination. None of the differences between the age groups were statistically significant.

All eight patients with detectable serum pentobarbital levels at the time of death had a CPP equal to zero. Seven of these patients had absent cerebral blood flow documented with

| | 2-12 mo | 1-5 y | >5 y |
|---------------------------------------|-----------|------------|-----------|
| Total No. of patients | 11 | 11 | 23 |
| Hours of observation,* median (range) | 28 (6-95) | 41 (6-143) | 41 (6-195 |
| Deep tendon reflexes | 0† | 3 | 7 |
| Spinal reflexes | 0† | 3 | 10‡ |
| Thermal instability | 7 | 6 | 11 |
| Diabetes insipidus | 0 | 0§ | 5‡ |
| Hyperglycemia | 9 | 7 | 19 |
| Inotropic support | 10 | 6 | 22‡ |

^{*}Hours of observation from time of first examination consistent with brain death and declaration of death.

- †Significantly less frequent (P<.05) than in older children.
- ‡Significantly more frequent (P<.05) than in younger children.
- §One patient had renal failure.

four-vessel arteriography. The eighth patient had absent cerebral blood flow documented with a radionuclide scan.

Twenty patients (51%) had autopsies. The neuropathologic findings are described in Table 3. Macroscopic observations in the majority of cases included dusky discoloration, cerebral edema (100%), diffuse softening (65%), and herniation of the temporal lobe unci and cerebellar tonsils (84%). The pathologic findings were similar regardless of age. Softening was present in one case after only 14 hours of observation before the declaration of brain death, as well as in the brains of individuals observed for the longest periods. Conversely, no softening was apparent in the brains of some individuals whose observation periods were as long as 41 hours. Four of the autopsies were on patients with detectable serum pentobarbital levels at death, and three of the four patients had moderate to severe cerebral softening.

There were no clear factors associated with the neuropathologic assessment of the severity of cerebral edema. Severe cerebral edema was seen at autopsy after as little as 14 hours of observation, while one child supported for 95 hours had only mild cerebral edema at autopsy. The CPP was not predictive of the neuropathologic assessment of cerebral edema. Eight of nine patients whose CPP was zero before death showed moderate to severe cerebral edema. Similarly, four of six patients whose CPPs were always greater than zero had moderate to severe cerebral edema. All four patients who had detectable serum pentobarbital levels at the time of death showed moderate to severe edema at autopsy.

Vascular changes secondary to herniation were seen infrequently (22% [4/18]). These changes included midline hemorrhages of the rostral brain stem with or without hemorrhagic infarcts in the distribution of the posterior cerebral arteries.

Microscopically, the majority of cases were characterized by edema of the neuropil, diffuse liquefactive necrosis, and absence of inflammatory or glial reaction. Neuronal signs of anoxia (ie, shrinkage of the nucleus and intense eosinophilia of the perikaryon) were present in 89% (17/19) of the brains. These changes were present throughout the cerebral cortex, basal ganglia, hippocampus, brain stem, and cerebellum.

Seven patients had pituitary abnormalities that were studied at autopsy. None of the patients had DI. Four specimens were histologically normal (patients 3, 6, 11, and 16 in Table 3). Patient 11 had hemolytic-uremic syndrome, was anuric, and thus could not be properly evaluated for DI. Patient 6 received vasopressin terminally but did not fit our definition of DI. One patient each showed mild, moderate, and severe anoxic changes (patients 8, 2, and 17, respectively). Unfortunately, none of the five patients with documented neurogenic DI had pituitary abnormalities studied at autopsy.

COMMENT

Although a consensus opinion was recently reached that suggested that

| | Observation | Cerebral | | Cerebral | Cerebral | Neuronal | | Vascular | Primary |
|--------------------|-------------|------------|-----|----------|-----------|----------|------------|----------|---------------|
| Patient No./Age | Period, h | Blood Flow | EEG | Edema | Softening | Anoxia | Herniation | Changest | Lesion |
| 1/4 mo | 28 | Absent | ECS | 3+ | 3+ | 3+ | None | None | Anoxia |
| 2/4 mo | 34 | Absent | ECS | 2+ | 1+ | ND | U,T | ND | Hemorrhage |
| 3/5 mo | 10 | NP | ECS | 2+ | 2+ | 1+ | None | None | Anoxia |
| 4/5 mo | 95 | Absent | ECS | 1+ | 2+ | 3+ | U | None | Trauma |
| 5/7 mo | 45 | NP | ECS | 2+ | 2+ | 3+ | T | None | Trauma |
| 6/10 mo | 6 | NP | ECS | 1+ | None | 3+ | U,T | None | Anoxia |
| 7/11 mo | 21 | NP | ECS | 3+ | None | None | None | None | Strangulation |
| B/1 y | 28 | NP | ECS | 3+ | 3+ | 3+ | T | None | Anoxia |
| 9/2 y | 42 | Absent | ECS | 3+ | 1+ | 3+ | Т | Yes | Trauma |
| 10/2 y | 41 | Absent | ECS | 3+ | None | 3+ | Т | None | Trauma |
| 11/2 y | 14 | Absent | NP | 3+ | 3+ | 3+ | U | None | HUS |
| 12/5 y | 49 | Absent | ECS | 3+ | 3+ | 3+ | ND | None | Anoxia |
| 13/5 y | 32 | Absent | NP | 2+ | None | 3+ | Т | Yes | Anoxia |
| 14/6 y | 45 | Absent | ECS | 3+ | ND | 1+ | U,T | ND | Anoxia |
| 15/6 y | 40 | Absent | ECS | 2+ | 2+ | 3+ | т | None | Anoxia |
| 16/9 y | 13 | Absent | ECS | 1+ | None | None | None | None | Vasculitis |
| 17/10 y | 55 | Absent | ECS | 3+ | 3+ | 3+ | U,T | Yes | Anoxia |
| 18/12 y | 149 | Absent | NP | 3+ | 3+ | 3+ | U,T | None | Trauma |
| 19/15 y | 23 | NP | NP | 2+ | 3+ | 1+ | U | Yes | Tumor |
| 19/15 y 20/16 y | 23 27 | NP | ECS | 1+ | None | 3+ | U | None | Anoxia |

*EEG indicates electroencephalogram; ECS, electrocerebral silence; U, uncal herniation; T, tonsillar herniation; ND, not specifically determined; NP, not performed; HUS, hemolytic-uremic syndrome; 1+, mild; 2+, moderate; and 3+, severe.

†Vascular changes are secondary to herniation.

children younger than 1 year require more stringent criteria of brain death,² other published criteria for children make no distinctions by age.⁴ Neither position is supported by published data.¹¹⁻¹⁵

This report addresses the issue of whether the physiology of brain death differs in young children. The age distribution of brain-dead children in this report is similar to the age distribution of previously reported brain-dead children compiled from the literature by Ashwal and Schneider. Spinal reflexes and deep tendon reflexes were found significantly less frequently at the time of brain death in children younger than 1 year. Additionally, DI was significantly absent in children younger than 5 years.

An interesting paradox, seen previously, 16,17 is the discrepancy between cerebral blood flow and ICP. Four brain-dead children who had absent cerebral blood flow documented by radionuclide brain scan never had ICP measured below 40 mm Hg. Ashwal and Schneider 17 suggested that several mechanisms for loss of cerebral blood flow must occur other than increased ICP. Another explanation for the par-

adox is that ICP measured on the dural surface (with a subarachnoid bolt) or in the supratentorial cerebrospinal fluid (with an intraventricular catheter) does not reflect pressures near the base of the brain where the major vessels enter the skull.

While the onset of DI has been suggested as a clinically useful sign of brain death, ¹⁶ we found DI to be an uncommon characteristic of brain death in children. Although infants can develop DI from a variety of causes, ¹⁹ no child in our series aged 5 years or younger developed DI despite the fact that half of the group had observation periods longer than 24 hours. Furthermore, only 22% (5/23) of children older than 5 years developed DI. Adults also do not universally have DI at the time of brain death. ⁶

The discrepancy between these data and those of Outwater and Rockoff, ¹⁸ who found 14 of 16 brain-dead children to have DI, probably relates to the more stringent definition of DI used in our study. Many factors may mimic DI in the severely head-injured patient. Excluded were children who developed a nonketotic, hyperglycemic osmotic diuresis (either secondary

to intravenous fluid administration or steroid therapy) or therapeutic diuresis from mannitol or furosemide administration.²⁰ However, about half of the children in this study never developed diuresis.

The neuropathologic observations agree with previous reports on the pathologic findings of brain death in adults and children. 21.22 Brain swelling, diffuse softening, liquefactive necrosis, discoloration, and herniation (a combination of changes also referred to as "respirator brain"21) were present as early as 14 hours after brain death. This interval is shorter than previously described. 22 Gross and microscopic changes appear to be stereotyped and independent of the nature or length of the primary process that led to brain death.

It can be correctly argued that once brain death is declared and cardiorespiratory support removed, recovery of neurologic function is precluded.^{23,24} However, no child in our PICU has fulfilled brain-death criteria (and then been hemodynamically supported for any reason) who recovered neurologic function even to the persistent vegetative state. Furthermore, because of

ethical, social, economic, and possibly statistical constraints,25 it is no longer feasible to directly validate braindeath criteria in children by supporting a large group of children who met brain-death criteria until irreversible cessation of cardiovascular function.

Most significantly, we found no evi-

dence that observation of the young brain-dead child between 2 months and 1 year old, beyond the accepted 12-hour period, provided any diagnostic advantage. Specifically, seven of the 11 children younger than 1 year who were observed from 24 to 95 hours while brain dead had no return of

neurologic function. We found no support for using different brain-death criteria for children between 2 months and 1 year old.

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In other AMA Journals

ARCHIVES OF DERMATOLOGY

A Child With Erythematous and Hyperkeratotic Patches

Judith T. Luy, MD; Alvin H. Jacobs, MD; Brian J. Nickoloff, MD, PhD (Arch Dermatol 1988;124:1271-1276)

Twins and Triplets With Necrotizing Enterocolitis

LTC Thomas E. Wiswell, MD, MC, USA, CAPT Charles T. Hankins, MD, MC, USA

• We reviewed 2856 multiple-gestation pregnancies from 1980 to 1985 to identify whether birth order or other features (eg. asphyxia) were significant risk factors for the development of necrotizing enterocolitis (NEC). There were 42 Infants identified as having NEC from 30 pairs of twins and three sets of triplets. The firstborn was diagnosed with NEC in 19 (45%) of the cases, with the disorder occurring in the secondborn in 23 cases (55%). While Infants A and B were simultaneously affected in nine cases, among the three sets of triplets, no thirdborn infants developed NEC. Although the secondborn infants had significantly lower one-minute Apgar scores and a more frequent need for resuscitation, they were no more prone to develop NEC than were firstborn infants. Multiple gestation, birth order, feeding practices, and a number of other features we evaluated were not associated with the development of NEC. Our findings support the contention that prematurity is the only consistent risk factor in the development of NEC.

(AJDC 1988;142:1004-1006)

Necrotizing enterocolitis (NEC) is a common disorder among premature infants.1,2 Except for prematurity, no consistent risk factors are associated with NEC.1-8 Premature birth is common among infants of multiple gestation.4.5 The largest report concerning infants of multiple gestation in which at least one infant had NEC described 13 instances of the disorder among ten pairs of twins and one set of triplets.6 This report revealed, surprisingly, that firstborn infants had a significantly higher occurrence of the disorder. These findings differed from our own clinical experience and that of others. 7,8 The latter two reports each described seven infants of multiple gestation with NEC. Because these study populations were all small, they

may not accurately reflect the characteristics of NEC among twins and triplets.

We hypothesized that there would be no difference in the occurrence of NEC based on birth order or other potential risk factors. This study was designed to test our premise.

PATIENTS AND METHODS

We examined the medical records of all infants with NEC who had been born and treated in US Army hospitals worldwide during the period from Jan 1, 1980, through Dec 31, 1985. This information was obtained through the US Army Patient Administration Systems and Biostatistics Activity at Fort Sam Houston, Tex. In the initial review of data, dates of hospitalization, gestational ages, and all diagnoses made were evaluated. Once infants of multiple gestation with NEC were identified, individual hospitals were contacted, and inpatient records of these infants and their concurrently born siblings were obtained and reviewed.

We defined a case of NEC as an illness in an infant fulfilling the modified Bell's staging criteria for definite or advanced NEC.9.10 Affected infants had to have clinical signs and symptoms of NEC, as well as definitive roentgenographic and/or pathological findings. Gestational ages for all newborns were determined from the maternal menstrual history and confirmed by physical and neurological findings.11 Smallfor-gestational-age and large-for-gestational-age infants were defined by birth weights less than the tenth or greater than the 90th percentiles for gestational age, respectively.12 We defined an epidemic of NEC as four or more episodes of the disorder during any three consecutive months in each particular facility.

Data were evaluated for significance using x2 analysis, two-tailed Fisher's exact probability test, and Student's t test, where applicable. P≤.05 was considered statistically significant. Because multiple comparisons were made between groups, Bonferroni's correction was used to decrease the likelihood of a type I error.

RESULTS

During the six-year period of the investigation, 264789 infants were born in US Army hospitals. Of these, 17456 were premature (≤37 weeks' gestation). There were 5648 twins (1976 premature) and 96 triplets (90 premature). Of the 338 total cases of NEC during this period, 295 infants were premature (16.9 of 1000 premature births and 0.17 of 1000 term births). Forty-two cases of NEC were diagnosed among 30 pairs of twins and three sets of triplets (20.3 of 1000 premature twins and triplets). Thirteen of 42 patients with NEC were ill during epidemics at various hospitals. These figures probably underestimate the frequency of NEC among US Army hospital-born infants. In several of the smaller military hospitals, neonates who are more than moderately ill are transferred to the nearest civilian level III nursery rather than to more distant government centers.

Eight of the 30 pairs of twins and one of the sets of triplets were black, reflecting the same racial proportions of premature infants born in US Army hospitals. None of the 42 affected infants was of term gestation. Of these children, in ten cases only the firstborn (infant A) had NEC, while infant B was solely affected in 14 cases. Infants A and B were simultaneously affected in nine cases. None of the three thirdborn triplets developed NEC. Twelve of the 42 neonates had positive blood cultures, and only one had not been fed before the onset of clinical symptoms. Selected characteristics of the infants and their siblings. as well as multiple potential risk factors, are presented in Tables 1 through 4. Tables 1 and 2 compare infants of different birth order, while Tables 3 and 4 compare those with NEC with those who did not develop NEC. The clinical data from two stillborn infants (one A and one B) were excluded from the tables and from subsequent analysis.

The statistically significant findings included the following: (1) secondborn infants had lower one-minute Apgar scores than firstborn infants (P < .01); (2) secondborn infants needed resuscitation more frequently than firstborn infants (P < .05); and (3) infants with NEC had positive blood cultures more frequently than those without

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the disorder (P<.005). Birth order, lower Apgar scores, or feeding practices did not predict which infants would subsequently develop NEC. We could not identify any predisposing risk factor that occurred significantly more often in infants with NEC.

COMMENT

Necrotizing enterocolitis is the most frequent serious gastrointestinal emergency encountered during the neonatal period. 1,2,9 The majority of infants with the disorder are premature.1-3 Many perinatal events seem to predispose to NEC (eg, asphyxia and the presence of umbilical catheters). However, several controlled investigations have failed to identify any consistent risk factor other than prematurity.1,3,8,13,14 These "events" are common to all sick, low-birth-weight infants. Kanto et al15 recently found that maternal toxemia during pregnancy was inversely related to the rate of NEC. We found no such association in this study, perhaps due to the relatively small population of affected infants.

Infants of multiple gestation are more likely to be born prematurely than are singleton infants. 4.5 In addition, it is well known that the secondborn twins more frequently have asphyxia and respiratory distress. 4.5 A reasonable expectation would be that B infants have a higher incidence of NEC. Samm et ale reviewed the histories of 13 infants with NEC who had been born of multiple gestation, the largest previous report evaluating birth order as a risk factor. These authors unexpectedly found that firstborn twins had a higher occurrence of NEC than their secondborn siblings. They speculated that differences in feeding practices (earlier initiation and more rapid progression in volume and concentration) may have contributed to the higher frequency of NEC in firstborn neonates. In contrast, Stine7 and Yu and Tudehope8 each described seven infants of multiple gestation with NEC. In both reports, four of the affected neonates were secondborn infants. In our investigation, birth order was not a risk factor for NEC among twins and triplets.

Kliegman and Walsh² reported un-

Table 1.—Basic Demographic Data Based on Birth Order in 30 Pairs of Twins and Three Sets of Triplets in Which at Least One Infant Had Necrotizing Enterocolitis*

| Feature | Firstborn | Secondborn | Thirdborn |
|---------------------------|--------------------|--------------------|--|
| Born alive | 32 | 32 | 3 |
| Stillborn | 1 | 1 | 0 |
| Gestational age, wk | 31.6 (26-37) | 31.6 (26-37) | 32.3 (28-37) |
| Birth weight, g | 1556 (631-3062) | 1491 (709-2400) | 1763 (1460-1898) |
| Apgar scores | | | |
| 1 min† | 6.4 (1-9) | 4.9 (0-8) | 7.3 (6-8) |
| 5 min | 7.7 (1-9) | 6.9 (1-9) | 8.3 (7-9) |
| Need for resuscitation‡ | 10 | 19 | 0 |
| Maternal toxemia | 2 | 2 | 0 |
| Sex | | | |
| M | 20 | 18 | 2 |
| F | 13 | 15 | 1 |
| Small for gestational age | 6 | 5 | 4.00 (1) (1) (1) (1) (1) (1) (1) (1) (1) (1) |

^{*}Values represent numbers of infants unless otherwise indicated. Values for gestational age, birth weight, and Apgar scores are means (ranges).

Table 2.—Postnatal Characteristics Based on Birth Order in 30 Pairs of Twins and Three Sets of Triplets in Which at Least One Infant Had Necrotizing Enterocolitis (NEC)

| | , | No. of Infants | |
|---|---------------|----------------|---------------|
| Feature | Firstborn | Secondborn | Thirdborn |
| Respiratory distress None | 11 | 7 | 2 |
| Oxygen alone | 5 | 6 | 0 |
| Mechanical ventilation | 16 | 19 | 1 |
| Umbilical catheter | 19 | 20 | 1 |
| Patent ductus arteriosus | 7 | 7 | o |
| Exchange transfusion | 0 | 3 | 0 |
| Polycythemia (hematocrit, 0.65) | 0 | 1 | 0 |
| Preceding hypoglycemia (serum glucose, <1.6 mmol/L) | 2 | 1 | 0 |
| Positive blood culture | 8 | 4 | 0 |
| First day fed* | 3.7 (0-33) | 4.7 (0-18) | 4.0 (1-10) |
| Day when volume of feeding reached 100 mL/kg* | 7.6 (2-37) | 8.5 (2-23) | 7.0 (1-12) |
| Day when first fed full- strength formula* | 8.2 (0-37) | 9.4 (2-28) | 8.1 (1-13) |
| No. with NEC | 19 | 23 | Ò |
| Deaths due to NEC | 3 | 3 | 0 |

^{*}Values are expressed as mean (range) day of life.

published data that support the theory that feeding practices are related to NEC. Patients who developed NEC were fed greater volumes of formula and at a faster rate than age-matched controls. Goldman¹⁶ also believed that feeding practices are important in the pathogenesis of NEC. In contrast, we

found no significant differences in time of first feeding or in advancement of volume or concentration of formula when we compared these factors among infants of different birth order and between those with NEC and those without NEC. To our knowledge, there have been no large, pro-

[†]Significant at P<.01. ‡Significant at P<.05.

Table 3.—Basic Demographic Data Comparing 42 Infants of Multiple Gestation Who Developed Necrotizing Enterocolitis (NEC) With Their Unaffected Siblings*

| Feature | Infants With NEC | Infants Without NEC |
|------------------------|--------------------|---------------------|
| Total No. | 42 | 25 |
| Gestational age, wk | 31.5 (26-37) | 31.8 (27-36) |
| Birth weight, g | 1534 (631-2420) | 1474 (709-3062) |
| Apgar scores 1 min | 5.8 (1-9) | 5.7 (0-9) |
| 5 min | 7.6 (3-9) | 7.0 (1-9) |
| Need for resuscitation | 19 | 10 |
| Maternal toxemia | 2 | 2 |
| Sex M | 23 | 15 |
| F | 19 | 10 |

^{*}Values represent numbers of infants unless otherwise indicated. Values for gestational age, birth weight, and Apgar scores are means (ranges).

Table 4.—Postnatal Charcteristics Comparing 42 Infants of Multiple Gestation Who Developed Necrotizing Enterocolitis (NEC) With Their 25 Unaffected Siblings

| 2002년(1907년 - 1907년 - 1940년 - 1957년 | No. of Infants | | | |
|--|------------------|---------------------|--|--|
| Feature | Infants With NEC | Infants Without NEC | | |
| Respiratory distress None | 12 | 8 | | |
| Oxygen alone | 7 | 4 | | |
| Mechanical ventilation | 23 | 13 | | |
| Umbilical catheter | 27 | 16 | | |
| Patent ductus arteriosus | 11 | 3 | | |
| Exchange transfusion | 2 | 1 | | |
| Polycythemia (hematocrit, 0.65) | 1 | 0 | | |
| Preceding hypoglycemia (serum glucose, <1.6 mmol/L) | 3 | 0 | | |
| Positive blood culture* | 12 | 0 | | |
| First day fed† | 4.0 (0-33) | 4.5 (0-14) | | |
| Day when volume of feeding reached 100 mL/kg† | 7.6 (2-37) | 7.8 (2-16) | | |
| Day when first fed full- strength formula† | 9.4 (0-37) | 8.6 (0-16) | | |
| Deaths | 8 | 3 | | |
| Deaths due to NEC | 6 | 0 | | |

^{*}Significant at P<.005.

spective, randomized investigations that have delineated the controversial relationship between feeding practices and the development of NEC.

The mortality rate from NEC in our 42 infants (14.3%) was low compared with other published reports. 1,3 However, we have found a mortality rate of 4.7% in 43 full-term infants with NEC and 11.9% in 295 premature infants with NEC. 17 We suspect that the lower mortality reflects an earlier aggres-

sive management compared with the earlier reports from the 1960s and early 1970s.

There is no unifying theory for the pathogenesis of NEC. Several of the following features are found in most affected infants: (1) relative immaturity of the gastrointestinal tract (most infants are premature); (2) a history of potential ischemic events (eg, asphyxia, respiratory distress); (3) implication of an infectious process (pos-

itive blood cultures, occurrence of epidemics); and (4) a history of having been fed (NEC is far less common in infants who have never been fed). These four features frequently are found in a population of sick, low-birth-weight, premature infants. There appear to be no unique factors that clearly distinguish the children who develop NEC.

We have examined the relationship of diverse factors in the pathogenesis of NEC among infants of multiple gestation. Our findings further substantiate the lack of identifiable risk factors for this potentially lethal disorder.

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[†]Values represent mean (range) day of life.

Book Review

Ethical Issues at the Outset of Life, vol 3 of Contemporary Issues in Fetal and Neonatal Medicine, edited by W. B. Weil, Jr, and M. Benjamin, 286 pp. \$45, Boston, Blackwell Scientific Publications Inc, 1987.

This is a worthwhile attempt to initiate a comprehensive framework for ethical issues at life's outset as they are affected by a burgeoning technology of procreation.

Leading authors cover the beginnings of life, organized in sequence: preimplantation, intrauterine, and postnatal. Following this are discussions of perinatal policy in a pluralistic society, ie, comparative anthropolitical perspectives and a discussion of the complexities of translating moral perspectives into social policy.

The editorial effort rests on three strong legs—the quality of the contributors, the developmental approach to life's beginning, and the capping section on policy formu-

lation.

The "Baby M" case, which pitted interests of the surrogate mother against those of gamete donor and contracting parents, has made familiar the conflicts between the interests of various sorts of "parents." Less discussed are ethical implications in creating multiple embryos. The fact that termination of pregnancy is the preponderantly available intervention after fetal genetic diagnosis is well known. Less appreciated is the increasing jeopardy to pregnant women's freedom as therapeutic benefits to the fetus and fetal effects of maternal habits become increasingly known.

John Arras' and Carson Strong's are discussions helpful to physicians struggling with difficult cases in neonatal

care.

Arras demonstrates that quality-of-life considerations are embedded in categories of conditions for which withholding or withdrawing of care from newborns is universally recognized even by those categorically rejecting quality-of-life judgments. Comparative judgments evaluate an infant's life against norms based on lives without disability or illness. Noncomparative judgments focus on an infant's condition and likely effects on the infant of proposed medical interventions. The former risks discrimination against the handicapped; the latter concentrates on a child's best interests. Arras makes possible a proper consideration of quality-of-life judgments that caretakers know are inescapable, while offering appropriate limits.

Dr Strong argues well that primary dedication to an infant's care and best interest also carries obligations to others; while dedication to an infant's life cannot be compromised, humane care demands tender care of the family, eg, discontinuing life support to a dying infant might be

briefly delayed to give the family time to adjust.

Dr Strong argues correctly that the proper locus for decision making in neonatal cases is parents with physician, giving some credit to ethics committee review to educate and counsel. While he generally leads to appropriate resolution of roles and responsibilities, his opening development seems to set up rigid categories of jurisdiction. Strong seems to imply that if the state were to have interest in guaranteeing just treatment to each infant, it would arrogate all responsibility from parents. As he develops the theme, however, he better captures the concept that is a prevailing consensus: parents are given broad discretion to decide for children in most matters but may not abuse them; in matters of life and death, they are deemed to be clearest about their children's best interests, but such

decisions, even if in agreement with the physicians, may be reviewed properly.

A fundamental thematic issue throughout, creating conflict or resolution of issues, is the moral status of the embryo, fetus, or newborn, a crucial issue in determining ethical limits of procreative practices, yet agreement appears to be elusive. Dr Robert Hahn's contribution, illustrates diversity of world views that condition moral status in various societies within the plurality in the United States. One extreme of contingency is developed by Dr Peter Singer in his contribution. He argues that embryos are singled out for protection due to "morally relevant differences . . . those based on our superior self-awareness, our rationality, our moral sense, our autonomy." Singer not only makes a case for limited moral status and limited protection of life for embryos and fetuses but also newborns lacking the aforementioned qualities early in development or capacity to appreciate and therefore possess "interests."

Perhaps Arras contradicts Singer: "the important ethical canon, the principle mutual concern and respect, that says that all human beings (or persons) ought to be accorded, if not equal outcomes, at least equal concern and respect in the allocation of benefits and burdens." Arras argues that we ought to be no more willing to terminate life-sustaining treatment for impaired newborns than for elderly patients suffering serious physical and mental disabilities: "It would amount to applying two different moral standards to groups that do not differ in any morally relevant respects and would, in short, yield an unfair and discriminatory moral

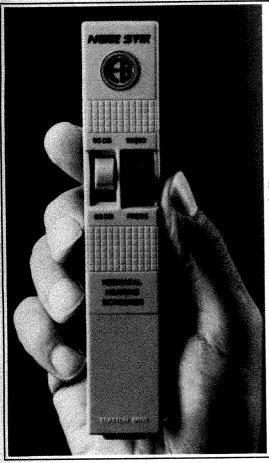
practice."

Notably, no author treating maternal-fetal issues refers to the human fetus as a human being, except possibly Dr Thomas Murray, who states that "many of us might be convinced that abortion is the wrongful taking of human life."

Murray makes a great contribution to comprehension of group dynamics in society's derivation of health care policy. It may be frustrating that ethical arguments cannot always be resolved into satisfying consensus, but that health policy must often go forward through compromise. The true meaning of compromise is discussed. Murray asserts that compromise appears integral to a world view and way of life we honor, enjoy, and defend "that explicitly recognizes a plurality of divergent and occasionally conflicting values and principles . . . that places a premium on understanding opposing viewpoints and positions, mutual respect, dialogue, weighing the consequences of our actions on others . . . that is presupposed by many of our democratic traditions and that recommends itself on pragmatic grounds to policymakers in an avowedly pluralistic society."

The editors have achieved their avowed purpose, ie, not to dispense authoritative conclusions but to enable more effective participation in ongoing discussions and debates. They look forward to eventual well-grounded, rational resolutions for some issues, and about others, the development of mutual understanding by those holding opposing views leading, where joint action is required, toward the development of mutually satisfying and workable compromise.

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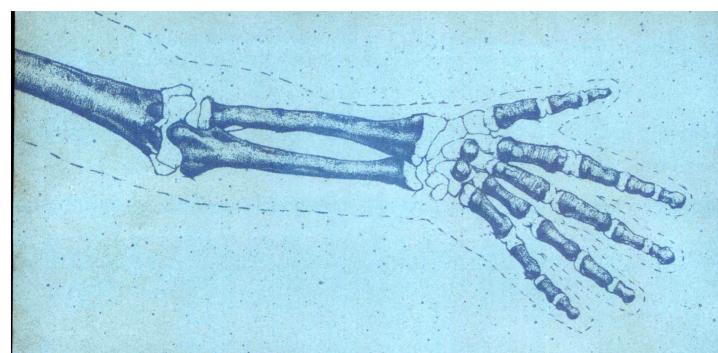
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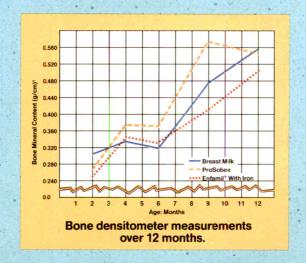


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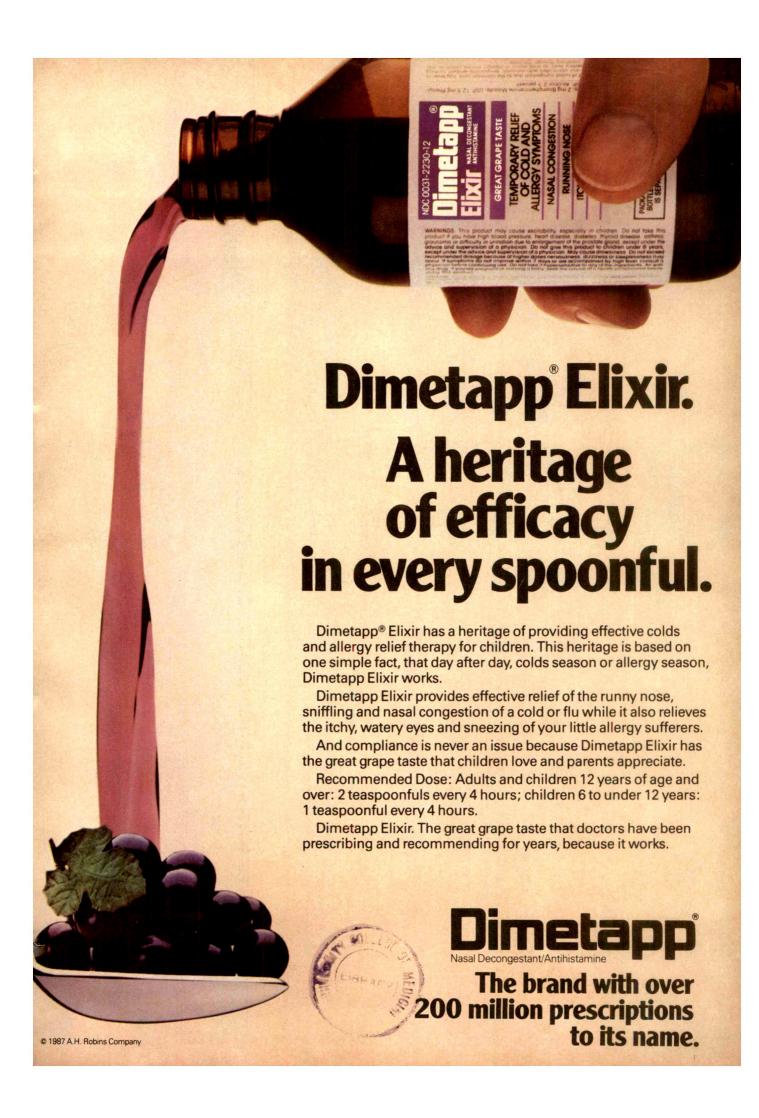
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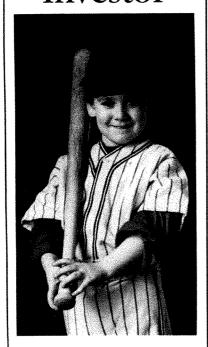
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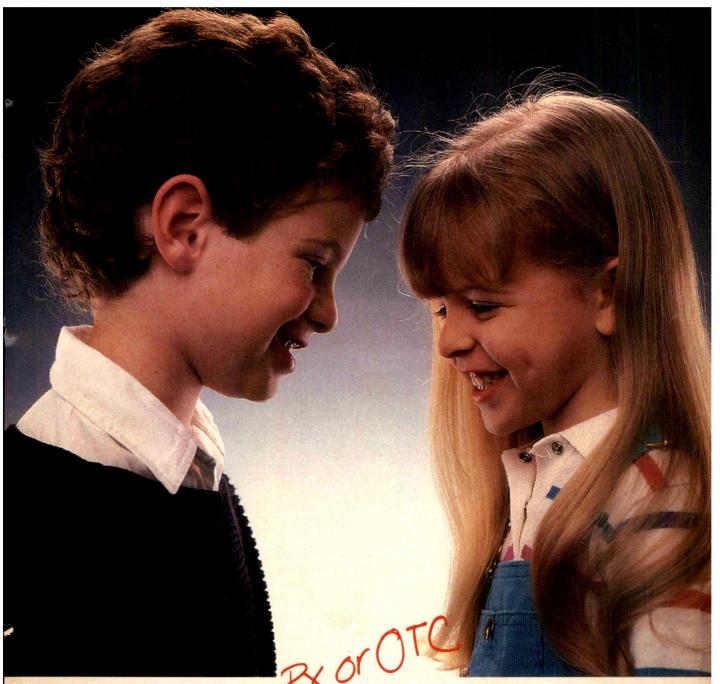
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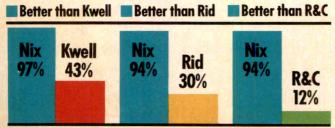
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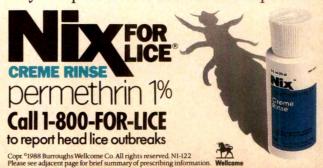
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Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of in vitro and in vivo genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired tertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp. Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic or other reasons.

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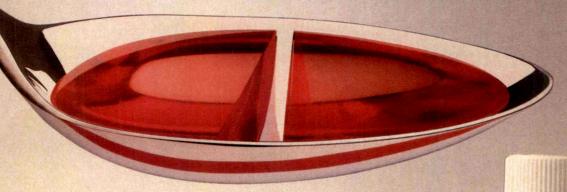
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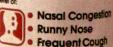
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The Pediatric Forum

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

Acute Appendicitis in Diabetic Children

Sir—Delayed chemotaxis, microangiopathy, and sensory neuropathy have each been implicated in the inability of adult diabetic patients to control acute inflammation. Experimental studies have demonstrated these same abnormalities in children with juvenile-onset diabetes mellitus, even though an increased susceptibility to infection is generally not apparent in these children. This retrospective analysis was undertaken to determine if juvenile-onset diabetes mellitus alters the course of acute appendicitis.

Patients and Methods.—From July 1959 to June 1983, 19 patients with type I diabetes mellitus underwent operation for acute appendicitis at the Montreal Children's Hospital. Seventeen case reports were suitable for analysis. The patients ranged in age from 4 years 5 months to 18 years, with a mean of 12 years 4 months. The diagnosis of diabetes mellitus had been made from five months to 131/2 years (mean, six years ten months) before appendectomy. The presenting symptom was right lower abdominal quadrant pain in 15 patients, right upper abdominal quadrant pain in one patient, and periumbilical pain in one patient. The preadmission duration of symptoms was three to 72 hours. All but three patients had peak temperatures below 38°C. White blood cell counts ranged from 8 to 21 × 10°/L, with a mean of 13.3×109/L.

Since the surgical and antibiotic treatment of acute appendicitis has differed from year to year since 1959, comparison of each of these 17 diabetic children was made with at least two and usually three age- and year-matched nondiabetic controls. Differences between the means of paired samples were then determined.

Results.—Seven patients (37%) with diabetes mellitus had a perforated appendix at the time of operation. Nondiabetic children treated at our institution for acute appendicitis during the same time period had an

| Comparison of the Presentation of Diabetic and Nondiabetic Children With Perforated Appendixes | | | | | | |
|--|-------------------------------------|----------|-----------|--|--|--|
| | Group | | | | | |
| | Juvenile-Onset Diabetes Mellitus | Controls | P* | | | |
| First symptom, % R lower abdominal quadrant pain | 85 | 5 | | | | |
| Periumbilical pain | 6 | 95 | | | | |
| Duration of preoperative symptoms, h | 39 | 72 | <.02 | | | |
| White blood cell count, ×109/L | 14.4 | 18.2 | <.05 | | | |
| Peak temperature, °C | 37.5 | 38.4 | <.01 | | | |

^{*}Difference between the mean of paired samples.

appendiceal perforation rate of 26% (P < .5). All patients underwent appendectomy at the initial operation, although the placement of drains and the use of antibiotics varied.

Comparison of the patients with diabetes mellitus with age-matched nondiabetic children disclosed several differences (Table). First, 85% of the diabetic children reported their initial symptom to be right lower abdominal quadrant tenderness, unlike 95% of nondiabetic children who complained of periumbilical discomfort that then localized to the right lower abdominal quadrant. Normal children with a perforated appendix at the time of hospital presentation related an average of three days of symptoms, whereas diabetic children averaged only 39 hours of abdominal symptoms. Mean white blood cell counts and peak temperatures for diabetic children with a perforated appendix were lower $(14.4 \times 10^9/L \text{ and } 37.5^{\circ}C)$ than in controls with a perforated appendix $(18.2 \times 10^{9}/L \text{ and } 38.4^{\circ}C)$.

Four (57%) of seven diabetic children with appendiceal perforation and 15 (79%) of 19 nondiabetic controls had peritoneal drains placed at operation and received seven- to ten-day courses of systemic antibiotics. Length of hos-

pitalization and the rate of postoperative complications were similar both for groups with perforation (10.8 vs 10.4 days, and 29% vs 16%) and those without perforation (4.6 vs four days, and 10% vs 9.6%).

Comment.—In 1978, Doraiswamy¹ concluded that acute appendicitis in children progresses from early to infected to complicated at one-day intervals. As expected during this progression, the white blood cell count and peak temperatures increase. This characteristic progression of acute appendicitis with its resulting signs and symptoms helps the clinician make an accurate and, it is hoped, early diagnosis. Children whose conditions fail to follow the natural history of acute appendicitis tend to have a delay in diagnosis and suffer the resulting complications. A prime example of this is acute appendicitis in children younger than 5 years of age who have a reported 62% perforation rate.2

Our retrospective analysis suggests that children with diabetes mellitus also diverge from the expected course of this disease. Minor derangements in the autonomic nervous system, capillary membrane permeability, and chemotaxis that are known to exist in diabetic children may explain the sub-

tle alterations we have found.

Early operative intervention in diabetic children suspected of having acute appendicitis will decrease the incidence of perforation with no increase in operative complications.

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- 1. Doraiswamy NV: Progress of acute appendicitis: A study in children. Br J Surg 1978; 65:877-879.
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Group A Streptococcal Carrier State

Sir.—Gerber et al1 raise important issues pertaining to identification of the group A streptococcal (GAS) carrier state. We agree that antistreptococcal antibody titers are of little value in distinguishing GAS carriers with intercurrent viral pharyngitis from patients with acute GAS infection. In addition to data presented by Gerber and colleagues, there is additional evidence that antibiotic therapy may blunt the immune response to bona fide GAS infection.2,3

Because we believe that in some circumstances there may be benefit to identifying and terminating the carrier state, we have considered various criteria to define chronic GAS carriage.4 In our treatment studies of such carriers, we have used a simple operational definition of GAS carriage that does not depend on assessment of serologic responses.4,5 We define a patient as a carrier if the patient is asymptomatic and the throat culture is still positive for group A streptococci three weeks after treatment with intramuscular benzathine penicillin G. We believe that this assessment reliably distinguishes streptococcal carriers from acutely infected patients. T-typing of pretreatment and posttreatment isolates has almost uniformly demonstrated persistence of the original T type in our patients with positive posttreatment cultures. Since there is no question of noncompliance with treatment and since penicillin is still present, the reisolation of the original streptococcal strain indicates that these patients are carriers.

In accord with the findings of Gerber et al,1 we have not found that serologic studies assist in this process. Although it is not necessary to identify carriers routinely, this method can be used when it becomes desirable to determine if a specific patient is a carrier.

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- 1. Gerber MA, Randolph MF, Mayo DR: The group A streptococcal carrier state: A reexamination. AJDC 1988;142:562-565.
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In Reply.-I agree with Tanz and Shulman that there is a need for an operational definition of the GAS carrier state, and, in fact, I have proposed an operational definition similar to the one they have used. I also agree that it is not necessary to routinely identify carriers, but there are some circumstances in which identification and termination of the carrier state would be desirable.1 These situations would include the following: families in which there is an inordinate amount of anxiety about GAS; families with a history of rheumatic fever; families in which "ping-pong" spread of GAS has been occurring; outbreaks of GAS pharyngitis in closed or semiclosed communities; and cases in which tonsillectomy is being considered only because of chronic carriage of GAS.

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Diphenhydramine Toxicity From Combined Oral and Topical Use

Sin-Diphenhydramine hydrochloride is used widely and is available in many nonprescription medications for both oral and topical use. During two months in the spring of 1987, three children were seen in the Primary Children's Medical Center (Salt Lake City) emergency department with varicella and a toxic encephalopathy from diphenhydramine. This occurred while they were taking appropriate doses of oral diphenhydramine (Benadryl) with concomitant liberal topical application of diphenhydramine (Caladryl) lotion (1% diphenhydramine hydrochloride, 2% alcohol and camphor).

Patient Reports.-Patient 1.-A 4year-old boy was well until he developed chickenpox three days before admission. His mother applied more than 90 mL of Caladryl in the 16 hours before admission. After administration of 3.75 mL of Benadryl elixir (0.6 mg/kg), he slept and was unarousable. When he awoke, he exhibited nonsensical speech that suggested that he was hallucinating. He was seen by a physician. A serum toxicology screen indicated the presence of tricyclic antidepressants.1 The boy became increasingly agitated, complained of difficulty urinating, did not recognize his mother, and was referred to the emergency department.

On examination, he was awake, but his speech was inappropriate. He weighed 16 kg, and had an axillary temperature of 36.6°C; his pulse rate was 104 beats per minute, respirations were 24/min, and blood pressure was 86/62 mm Hg. He had 7-mm reactive pupils, a flushed face, and a rash consistent with varicella. He was ataxic but had otherwise normal neurologic examination results.

Laboratory evaluation revealed normal electrolyte levels. His serum glucose level was 4.9 mmol/L; serum aspartate aminotransferase level, 65 U/L; y-glutamyltranspeptidase activity, 24 U/L; ammonia level, 54 µmol/L; and blood urea nitrogen level, 3.2 mmol/L. His urine toxicology screen was positive for diphenhydramine and pseudoephedrine. The plasma diphenhydramine level was 1.5 mg/L (toxic level, >0.6 mg/L), and the plasma tricyclic antidepressant levels were normal. His mental status returned to normal in less than 12 hours, and he was discharged.

PATIENT 2.—A 7-year-old boy with chickenpox of four days' duration presented after he awoke confused and screaming incoherently. He complained of pain yet would not let his parents examine or console him. On his way to the hospital, his mental status normalized, and he asked his parents where they were going. In the preceding 24 hours, he had received three doses of Benadryl (1.1 mg/kg), and he had applied Caladryl lotion "every time it

itched." His only other medication was dicloxicillin for a secondarily infected pox.

In the emergency department he was alert and cooperative and exhibited a normal mental status. He was amnestic about the screaming and kicking episodes and could not describe any hallucinations. His temperature was 36.3°C, heart rate was 104 beats per minute, respirations were 24/min, and blood pressure 92/56 mm Hg; he weighed 22 kg. His general physical examination and neurological examination yielded normal results, except for the skin lesions of varicella. He was discharged after observation in the emergency department. He had no further recurrences after discontinuation of the Benadryl and Caladryl.

PATIENT 3.—A 5½-year-old girl had developed varicella four days before her emergency department visit. In the 24 hours before presentation, she slept intermittently, and her parents described temperament changes and visual hallucinations. Caladryl was applied four times the previous day, and she had received Benadryl (1 mg/kg) two to three times daily for

the previous two days.

Physical examination revealed a scared girl who was hallucinating. Her temperature was 37.3°C, pulse rate was 116 beats per minute, respirations were 20/min, and blood pressure was 96/56 mm Hg; she weighed 19 kg. She had a rash consistent with varicella. Her pupils were dilated but reactive to light, and neurological examination revealed dysmetria, poor tandem walk, and a wide-based gait. The remainder of her neurological examination findings were normal. Her serum aspartate aminotransferase level was 66 UL; serum glucose level, 5.2 mmol/L; and diphenhydramine level, 0.96 mg/L.

She was discharged and recovered uneventfully after discontinuation of the

Benadryl and Caladryl.

Comment.—These patients demonstrate the potentially alarming situation of a child with varicella who exhibits mental status changes. The differential diagnoses include postvaricella encephalitis, febrile delirium, toxic encephalopathy, and Reye's syndrome. The clinical presentations above are consistent with reports of diphenhydramine toxicity.2-5 The diagnosis of a toxic encephalopathy is supported by the rapid resolution of symptoms with discontinuation of the diphenhydramine-containing medications and the demonstration of toxic levels in two of three patients. In each case, the family was administering appropriate doses of oral Benadryl with liberal topical application of Caladryl. Diphenhydramine toxicity due to the exclusive use of topical Caladryl has been recently reported.2.4

The physician should be alert to the

possibility of diphenhydramine toxicity when confronted with a child with varicella and acute mental status changes. Families and physicians should be advised against combined use of topical and oral diphenhydramine-containing preparations.

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Perspectives on the Relative Resurgence of Mumps in the United States

Sir.—In the May 1988 issue of AJDC, Cochi et al¹ described the problem of mumps resurgence in the United States, due to a relatively underimmunized cohort of children born between 1967 and 1977. This cohort has been developing mumps at an older median age than children in the prevaccine days. It is regrettable that this problem was allowed to develop, because it was predictable and could have been attacked at less expense when the children were much younger and easily identifiable as being susceptible. 2.3

Mumps is a disease subject to eradication. It is not highly contagious and has no animal reservoir. Mumps vaccine should have been provided by Centers for Disease Control, Atlanta, through its vaccine assistance program for low-income children in the early 1970s when it became apparent that the vaccine was being used widely by private health care providers for their patients and that this was changing the probabilities of natural expo-

sure to the virus. It seems ethically wrong that this did not happen. Moreover, the next time a vaccine is introduced for a childhood disease, we will probably see the same scenario and, again, it will not prove cost-effective to delay an appropriate immunization program for children who rely on local health departments for their immunizations.

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- 1. Cochi SL, Preblud SR, Orenstein WA: Perspectives on the relative resurgence of mumps in the United States. *AJDC* 1988;142:499-507.
- Bader MC: Mumps vaccination too costly for developed country. N Engl J Med 1973; 289:1255.
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In Reply.—Dr Bader raises an important issue that was the subject of some controversy for several years1,2 following the introduction of live attenuated virus mumps vaccine in the United States in December 1967. In retrospect, routine use of the mumps vaccine as soon as it was introduced might have prevented the circumstances that have led to the relative resurgence in mumps recently observed. Most expert opinions at the time of vaccine licensure, and for approximately ten years thereafter, did not recommend priority be given to mumps vaccination. Low priority for mumps vaccination was the result of a variety of factors, including doubts about the duration of immunity conferred by mumps vaccine in the absence of longterm efficacy data and a lack of epidemiologic data on the health impact of mumps that were as convincing as, for example, those for poliomyelitis, rubella, and measles.2 In the absence of strong recommendations, the Centers for Disease Control, as well as most state health departments, devoted the scarce resources available to control other higher-priority vaccinepreventable diseases. If resources had been diverted from control of measles and rubella to buy the most expensive vaccine at the time, mumps vaccine, there might have been more adverse outcomes from these more serious vaccine-preventable diseases. Furthermore, one must remember that the early 1970s was a different era in the history of federal support of publicsector immunization programs. This period preceded the intensified efforts, beginning in 1977, through the

National Childhood Immunization Initiative to achieve immunization levels in the nation's children of greater than 90% for all vaccine-preventable dis-

eases, including mumps.

Any live viral vaccine introduced for use primarily in preschool-age and young school-age children will result in a shift in the age distribution of the remaining cases toward older persons. This has been our experience with measles and rubella, as well as with mumps. However, the shift in age has been more dramatic for mumps than for the other two diseases. What is important is that this experience be seriously considered in the future when other new vaccines may be introduced for routine immunization against a childhood disease such as varicella. We can anticipate that a substantial portion of any undesirable change in the epidemiology of varicella might result from nonroutine vaccination of all healthy children. This practice could place older, unimmunized, susceptible persons with a higher likelihood of complications at risk for the disease.

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- Bader MC: Mumps vaccination too costly for developed country. N Engl J Med 1973; 289:1255.
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Cases of Mumps Following Previous Vaccinations

Sir.—Dr Pachman, in the May issue of AJDC, suggests that adolescents should receive a booster dose of mumps vaccine based on "a high incidence in the 10- to 20-year-old group, many of whom had been previously vaccinated in early childhood".

Dr Pachman does not tell us whether or not any of these cases of "mumps" were confirmed by acute and convalescent serologic studies. It is well known that other paramyxoviruses can produce a clinical picture that is indistinguishable from mumps. This fact and the problem of serologic confirmation of mumps were both addressed in the article by Cochi et al² in the same issue.

As the incidence of parotitis due to

mumps declines because of immunization, a greater proportion of parotid gland swellings will be attributed to the other viruses. I suggest that the epidemic of mumps that Dr Pachman reports may have been due to one of the other viruses.

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In Reply.—The statement by Dr Davis raises an important question. How can the physician, faced with a patient with acute parotid gland swelling, make an accurate clinical diagnosis? In the March 1979 issue of $AJDC^1$ I discussed the article by Biedel² entitled "Recurrent Mumps Following Natural Infection and Immunization.' I indicated that a confirmed diagnosis of mumps cannot be made without serologic studies for mumps virus as well as other viruses known to cause parotitis.

Early in the recent outbreak of mumps cases in Chicago (1986-1987) an attempt was made to collect blood samples from the acute and convalescent phases in my patients who had acute parotid gland swellings. However, the effort was abandoned because of lack of cooperation by the patients and the inability to obtain an accessible, competent laboratory.

In their recent report "Perspectives on the Relative Resurgence of Mumps in The United States" Cochi et al accepted any case report as being of mumps without laboratory confirmation, since at present there is an absence of a uniform clinical case definition. Until firm criteria for the diagnosis of mumps are achieved, physicians will be forced to make the diagnosis of mumps on a clinical impression.

In 1979¹ I wrote that the cooperation of physicians in practice with an agency such as the Centers for Disease Control in Atlanta is needed to resolve the problem of diagnosis and prevention of mumps. It is hoped that this can be achieved by the following means: (1) establishing accurate criteria for the diagnosis of mumps; (2) investigating outbreaks of parotid

gland swellings, such as has occurred recently in Chicago (1986-1987) with serologic and viral studies undertaken by established competent personnel; and (3) determining whether there is a need for booster doses of mumps vaccine in previously vaccinated children when they are exposed to the virus.

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Anaphylactic Shock to Old, Dissolved Immunoglobulin

Sir.—Therapeutic use of intravenous immunoglobulin has been recommended for the treatment of acute and chronic idiopathic thrombocytopenic purpura¹ and neonatal sepsis.^{2,3} For prophylactic purposes, we infused 0.5 g of intravenous immunoglobulin (Sandoglobulin, Sandoz LTD, Basel, Switzerland) into healthy premature infants with birth weights of 1500 to 2000 g. Freshly dissolved immunoglobulin solutions were used, but for economic reasons the remainder of two bottles of immunoglobulin solutions was not discarded. These residues were stored at -4°C to -10°C for five and six days, respectively. The frozen solutions were rethawed and warmed to room temperature just before use. On infusion into two premature infants, we observed two anaphylactic reactions; one was lethal.

Patient Reports.—Patient 1.—A 1-day-old male infant (birth weight, 1700 g) was given 0.5 g of five-day-old immunoglobulin solution. It was infused slowly, at a rate of about seven to eight drops per minute. The infant was followed up closely by one of us (F.K.). One hour after termination of the infusion, generalized redness, fever, skin edema, tachycardia, and respiratory distress were noted. The indied despite resuscitative measures. Histopathologic examination showed generalized congestion, vasodilation, and edema in internal and external tissues.

PATIENT 2.—The second bottle of

old immunoglobulin solution was administered to another premature male infant at the same time as the first infant's infusion. He was 3 days old, and his birth weight was 1870 g. Five hours after completion of the infusion, rash, generalized skin edema, and fever appeared. The infant experienced respiratory distress that necessitated resuscitation. His symptoms slowly disappeared within 24 hours.

Comment.—Two infants showed severe allergic reactions after infusion of old, frozen immunoglobulin solution. No bacteria were isolated from either solution or the blood of either infant. Neither infant had received immunoglobulin before. One unit of the freeze-dried preparation contains 1 g of protein and 1.67 g of sucrose as well as small quantities of sodium chloride, without any preservative. The manufacturer recommends that after the freeze-dried preparation has been reconstituted, it should be administered without delay, and opened bottles should not be used again because of the danger of bacterial contamination, but instructions do not refer to old, frozen-preserved immunoglobulin solution.

The exact cause of these anaphylactic reactions is not completely known. We speculate that aggregates of immunoglobulin were formed in the old immunoglobulin solution. Our experience suggests that intravenous immunoglobulin once prepared for infusion should not be stored for future use. Residual amounts should be discarded.

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Thyroid Scanning, Ultrasound, and Serum Thyroglobulin in Determining the Origin of Congenital Hypothyroidism

Sin—Muir et al' recently presented results of different diagnostic procedures to determine the cause of con-

| Comparison Between | en Our Results and Those of M | uir et al¹ | | |
|---|---|-----------------------|--|--|
| Diagnosis Based on the Radioactive Iodine 123 Scanning Result | Concordance Between Ultrasound Examination and Scan by Study, % | | | |
| | Muir et al' (n = 50) | Our Study (n = 78) | | |
| Athyrotic glands | 66.6 | 72.7 | | |
| Ectopic glands | 0.0 | 73.0 | | |
| Normally located glands | 93.4 | 95.8 | | |

genital hypothyroidism (CH).

We would like to comment on their conclusions in regard to our experience with radioactive iodine 123 scanning and cervical ultrasound (US) in 80 hypothyroid patients. An iodine 123 scan was performed at the initial visit (mean age, 19 days) and US examination was performed at 4 months of age. Cervical US examinations were performed and reviewed by the same interpreter, who was "blinded" to the result of the scan, as in the work of Muir et al.¹

Two patients were excluded because US was impossible since the children were restless during the examination. Considering the results obtained by ¹²³I scanning, 43 patients had ectopic glands; 11, athyrosis; and 24, normally located glands (NLGs).

Of 24 patients with NLGs, only one was initially diagnosed as being athyrotic on US. A second US examination concluded that the patient had NLGs. Of 43 patients with ectopic glands, four were thought to have NLGs on US and six were interpreted as athyrotic, but the ectopy was very small and visible only on the 24th-hour picture of the scan (a repeated US examination was able to localize ectopic tissue in one of these cases); no definite US interpretation was possible in the two remaining cases. Of 11 athyrotic patients, US results yielded a diagnosis of ectopic gland in two patients and NLGs in one patient (a repeated US examination revealed an ectopic gland).

In summary, concordance was obtained in 80% of the patients. Compared with the results of Muir et al, the most important difference concerns results in ectopic CH (Table). The better concordance in our group may be due to the larger number of patients (43 vs 13) and the age at which US examination was performed (4 months).

In conclusion, our findings are less

pessimistic than those of Muir et al. Indeed, US has three limitations: the lack of sensibility to detect small ectopic glands, the lack of information on thyroid hormonogenesis, and the need of the collaboration of a trained interpreter. Nevertheless, US is less invasive and can be proposed as a primary investigation, with nuclide scanning being proposed to solve borderline cases. Nuclide scanning can also result in misclassification,2 and the observation of failure to visualize thyroid gland, even in euthyroid children,3 may validate the US result in some patients classified as athyrotic on scanning and interpreted as ectopic on US. Serum thyroglobulin concentration may help to assess the presence or absence of thyroid tissue in such cases.4

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In Reply.—Farriaux and Dhondt suggest that US may be just as sensitive as radionuclide scanning to help determine the cause of CH in children. They were able to detect 73% of ectopic glands while we could not detect any. The reasons for this are not clear but

may relate to the sensitivity of the equipment or the fact that they scanned their patients at 4 months of age, whereas ours were examined at birth. The results in athyrotic children and in those with NLGs were similar to ours. We do not dispute their results but agree that US has the limitations that they indicate. We do not believe that the level of serum thyroglobulin is helpful. With further technical advances, US may replace radionuclide scanning. However, at the present time, we believe that radionuclide scanning remains the "gold standard" for diagnosing the cause of CH.

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Calcification of the Laryngeal, Tracheal, and Bronchial Cartilages in Children

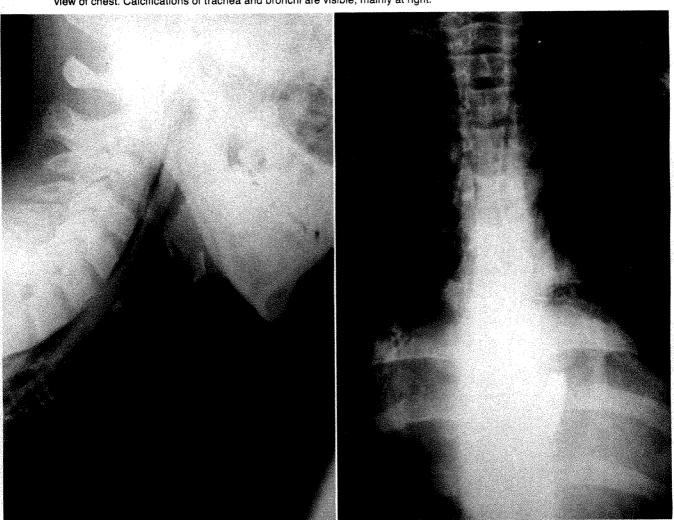
Sir.—Calcification of the larynx, trachea, and bronchi is rare in children. We describe two patients and review five other cases from the literature. Calcification is most often discovered in infancy because of stridor. The serum calcium level is normal. Laryngoscopy showed laryngeal rigidity in only two of seven cases. The clinical course is favorable. Tracheal and bronchial calcifications were present in the 35-year-old father of one patient and the 37-year-old mother of another patient.

Patient Reports.—Patient 1.—A 3-month-old infant had difficulty breathing with failure to thrive. At 9 months of age, laryngeal stridor was still present. Direct laryngoscopic examination, roentgeno-

grams of the esophagus, a sweat test, and muscle studies were performed, and results were normal. At 2 years, 8 months of age, his weight was 10.7 kg, and he measured 90 cm. Chest roentgenograms showed pneumonia in the right middle lobe. There was calcification of the laryngeal and tracheal cartilages. No other calcifications were found. The serum calcium concentration was normal. The father, aged 35 years, also had tracheal and bronchial calcifications.

Patient 2.—A boy was born with a congenital mitral stenosis and a coarctation. At 4 years of age, a mitral prosthesis (Starr valve) was inserted. On the chest roentgenogram, there was no calcification. At 15 years of age, calcifications (Figure) of the cartilages of the larynx, trachea, and bronchi were present without any clinical signs. A new prosthesis (Bjork valve) was inserted at 16 years of age, but the boy died of cardiac insufficiency. Autopsy showed that the cartilage annulus at the bifurcation of the trachea was partially

Patient 2. Left, Lateral view of neck. Note calcifications of thyroid, cricoid, and tracheal cartilages. Right, Frontal view of chest. Calcifications of trachea and bronchi are visible, mainly at right.



| Source, y | Sex/ Age S | | Associated Findings | Calcifications | | Blood Calcium and Phosphorus | Results of Laryngos- | Clinical | Family Members With | |
|---|---------------|-------------------------------------|---|----------------------------------|---------|------------------------------------|-----------------------------|---|--|-----------------------|
| | | Symptoms | | Larynx | Trachea | Bronchi | Concentrations | copy | Course | Calcifications |
| Nabarro, ⁵ 1952 | M/9 mo | Stridor | | Anterior: cricoid, thyroid | Yes | No | Normal | Normal | Unknown | •• |
| Russo and Coin, ⁶ 1958 | M/3 mo | Stridor, respiratory distress | Growth retardation, respiratory infections | Thyroid, cricoid | Yes | No | Elevated phos- phorus | Normal | Normal at 6.5 y of age | |
| Goldbloom and Dunbar, ² 1960 | M/4.5 mo | Stridor | ••• | Anterior: thyroid | Yes | No | Normal | Rigidity of larynx, tracheo- malacia | Normal at 2.5 y of age | 37-year-old mother |
| Marchal et al, ³ 1974 | F/10 mo | * * * | Septal defect | Thyroid | Yes | Yes (lobar) | Normal | Normal | Normal at 3 y of age | |
| Mlynarski et al,4 1985 | M/21 d | Stridor | ••• | Anterior: thyroid, cricoid | Yes | No | Normal | Normal | Stridor decreased at 1 y of age | *** |
| Present study Patient 1 | M/32 mo | Stridor | Growth retardation, respiratory infections | Anterior: thyroid, cricoid | Yes | No | Normal | Laryngo- tracheal rigidity | Regression of stridor, recurrent respiratory infection | 35-year-old father |
| Patient 2 | M/14 y | ••• | Congenital mitral insufficiency, coarctation | Cricoid, thyroid | Yes | Yes (lobar and segmental) | Normal | Not performed | Died of cardiac insufficiency after surgery | • • • |

calcified. The serum calcium concentration was always normal.

Comment.—Idiopathic calcifications are very rare in children, with the exception of calcifications of the hyoid cartilage. We found five reports of idiopathic calcifications. 2-6

In five of seven cases, stridor was present (Table). In two cases, there was a cardiac defect (one septal defect³ and our patient 2). In two cases, there were failure to thrive and recurrent respiratory infections (Russo and Coin⁶ and our patient 1). In two cases, another member of the family had calcifications, a mother aged 37 years² and a father aged 35 years (our patient 1).

Plain roentgenograms showed non-homogeneous calcifications of the cricoid and thyroid cartilages that mainly occurred in the anterior portion of the larynx. In the trachea, calcifications are regular and mainly occur anteriorly. Calcifications of the bronchi are rarer (two of seven cases).

Results of laboratory studies were negative. Laryngoscopy may show a rigid and slightly stenotic respiratory tract.

The clinical course is usually favorable, with regression of the clinical

symptoms and growth and increase of the caliber of the respiratory tract, as in patient 1. The calcifications remain unchanged.

The cause of these calcifications is unknown. Because cartilage elsewhere in the body has shown no premature or excessive calcification, we suspect that the lesion is basically a localized anomaly of the cartilage matrix that renders it more susceptible to calcium deposition. A generalized metabolic disturbance seems unlikely.

These calcifications are quite different from those associated with other diseases: (1) Chondrodysplasia punctata⁷⁻¹² is associated with calcifications of the larynx and trachea that gradually disappear by the second year of life. (2) The calcifications associated with idiopathic hypercalcinosis are different,13 including hypercalcemia, calcification of soft tissues, nephrocalcinosis, and an elfin facies. (3) Tracheopathia osteoplastica14-17 is a rare benign tumorous condition very seldom seen in patients under 30 years of age.18 A typical roentgenogram shows multiple flat, nodular, and calcified tumors involving the lateral and anterior walls of the trachea. (4) Degenerative calcification of larynx and

trachea is common in adults above 50 years of age. (5) Laryngeal calcifications have been reported in Keutel syndrome, adenogenital syndrome, and diastrophic dwarfism. 19

In conclusion, these seven children had a special, possibly familial, entity. Stridor is frequent but not constant and regresses with growth.

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Arm Support for Blood Pressure Measurement

Sin-Because it has become evident that children and adolescents have hypertension more often than was previously recognized,1 it is important that routine blood pressure measurement be as accurate as possible. An important factor that is often overlooked is the proper positioning and support of the forearm of the patient during a blood pressure determination.2 It has been reported that incorrect arm position can cause as much as a 10-mm Hg error in both systolic and diastolic pressures.3



Portable intravenous stand with adjustable wooden arm support used during pediatric blood pressure measurements

The American Heart Association recommends that the entire forearm be supported at heart level on a smooth surface during a blood pressure measurement.4 Standard positioning of the forearm at the horizontal level of the fourth intercostal space at the sternum is therefore recommended for blood pressure measurements with the patient in the sitting and standing positions.4

Adequate support of the forearm during blood pressure determination is often difficult to achieve because of the varying ages and heights of the patients examined in the pediatric setting. There may also be no available surface on which to rest the patient's forearm at heart level. We designed a mobile, adjustable arm support for use in the Hypertension Clinic of the Children's Hospital Medical Center, Cincinnati. A portable intravenous stand with an adjustable wooden arm support (17.5×45.5 cm) attached to the top (Figure) has provided adequate forearm support for our patients. For use with patients in the sitting or standing position, the support can be easily raised or lowered from 96 to 152 cm to allow for more precise adjustments for height. We have used this device in our pediatric hypertension clinic for two years and have found it quite useful. The ease of transporting the support from one examining room to another and the low cost make it practical for use in the clinic, hospital, or private practice setting.

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Elland and Bethesda avenues Cincinnati, OH 45229 1. Loggie JMH: Evaluation and management of childhood hypertension. Surg Clin North Am

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Anna L. King, RN

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The usual standard for blood pressure measurement in children is that it be taken in the right arm while the subject is sitting. How many of us do so? The device demonstrated in this letter should help with this standardization. Studies should be done to compare results obtained in the usual manner with those obtained from use of this device to see if its use is warranted. If results prove its usefulness, it should find its way into general use.

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Quotables:

Creation: If the Lord Almighty had consulted me before embarking on the creation I would have recommended something simpler. ALFONSO X OF CASTILE

Perspectives in Biology and Medicine 1985



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INDICATIONS AND USAGE: Tavist (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation. Tavist (clemastine fumarate) Syrup is indicated for use in pediatric populations (age 6 years through 12) and adults (see DOSAGE AND ADMINISTRATION).

It should be noted that Tavist (clemastine fumarate) is indicated for the relief of mild uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage lavet only.

CONTRAINDICATIONS: Antihistamines are contraindicated in patients hypersensitive to the drug or to other anti-

histamines of similar chemical structure (see PRECAUTIONS—Drug Interactions).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (see PRECAUTIONS—Nursing Mothers).

WARNINGS: Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction.

Use with CNS Depressants: Tavist (clemastine fumarate) has additive effects with alcohol and other CNS depressants (bypnotics, sedatives, tranquilizers, etc.)

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

ADVERSE REACTIONS:

The most frequent adverse reactions are underlined:

Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, termor, irritability, insommia, euphoria, paresthesia; blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nau-

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions,

tightness of chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Genitournary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION: DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

Pediatric: Children aged 6 to 12 years

For Symptoms of Allergic Rhinitis—The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 6 teaspoonsful daily (3 mg clemastine).

For Urticaria and Angioedema—The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily, not to exceed 6 teaspoonsful daily (3 mg clemastine).

Adults and Children 12 Years and over:

For Symptoms of Allergic Rhinitis—The starting dose is 2 teaspoonsful (1.0 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonsful daily (6 mg clemastine).

For Urticaria and Angioedema—The starting dose is 4 teaspoonsful (2 mg clemastine) twice daily, not to exceed 12 teaspoonsful daily (6 mg clemastine).

HOW SUPPLIED: Tavist (clemastine fumarate) Syrup: clemastine 0.5 mg/5 ml (present as clemastine fumarate 0.67 mg/5 ml). A clear, colorless liquid with a citrus flavor, in 4 fl. oz. bottle (NDC 0078-0222-31).

Store and dispense: Below 77°F (25°C) tight, ember glass bottle. Store in an upright position.

TAS-Z3 4/1/86]



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Leads From the MMWR

Morbidity and Mortality Report Centers for Disease Control, Atlanta

Progress Toward Achieving the 1990 Objectives for Pregnancy and Infant Health

THE 1990 HEALTH Objectives for the Nation, published by the Public Health Service (PHS) in 1979, included 19 objectives related to pregnancy and infant health. PHS identified 13 of these as "priority objectives" for federal programs and activities. These objectives concern improving the health status, reducing risk factors, increasing public and professional awareness, and improving health services and protection for mothers and infants.

Despite numerous public and private efforts, current projections for 1990 indicate that the majority of objectives for improving health status and reducing risk factors for pregnant women and infants will not be met. The decline in the infant mortality rate (IMR) has slowed since the preceding decade, and no progress has been made in reducing low birthweight (LBW)—less than grams. Between 1970 and 1981, the IMR in the United States declined by nearly 5% per year. Between 1981 and 1985, the decline slowed to less than 3% per year. Based on estimates of the National Center for Health Statistics (NCHS), recent rates now exceed the confidence limits estimated from the 1970-1981 trend. The 1970-1981 trend projected the 1990 IMR to be 7.8 per 1,000 live births. The 1981-1985 trend projects a 1990 IMR of 9.1 per 1.000 live births. In addition, the 1970-1981 trend analysis projected that 41 states would meet the 1990 objective of no more than nine deaths per 1,000 live births. The 1981-1985 analysis projects that 25 states will meet this objective.

Between 1970 and 1985, IMR has

decreased by 50% and LBW rate by 15%. Thus, most of the progress in reducing infant mortality over the past 15 years has resulted from a decline in birthweight-specific mortality; that decline, in turn, is likely due to technologic improvements in perinatal care. The LBW rate (6.8%) was the same in 1980 and 1985. The incidence of very LBW infants (less than 1,500 grams at birth) has been increasing in recent years. The 1990 LBW projection of 6.7% is 35% higher than the objective.

Programs to promote the use of infant safety seats in automobiles have been successful.

National survey results indicate that pregnant women and women who have recently been pregnant are more knowledgeable about smoking and alcohol risks than are members of the general population 18 to 44 years of age.

Progress has been made in one of the four priority objectives for improving services and protection: all states have screening programs for newborns. In 1980, 73.3% of pregnant women received first-trimester prenatal care, and in 1985, 76.2% received such care. Recent studies confirm that access to care remains inadequate for many women.⁷

Reported by: Office of Maternal and Child Health, Bureau of Maternal and Child Health and Resources Development, Health Resources and Services Administration. Office of Disease Prevention and Health Promotion. National Institute of Child Health and Human Development, National Institutes of Health. National Center for Health Statistics; Div of Reproductive Health, Center for Health Promotion and Education, CDC (MMWR vol 37, No. 26).

CDC Editorial Note: The Low Birthweight Prevention Work Group, formed in 1984 with representation of experts on maternal and infant health from organizations within the Department of Health and Human Services, has served as the focus and coordinating body within the federal government for service, research, and information efforts to address LBW and other causes of infant mortality in the United States.

Efforts to improve coordination and effectiveness of health services have intensified. The National Governors' Association and HRSA are collaborating to assist states in implementing the current expanded Medicaid eligibility and coverage options. In a related activity, the Health Care Financing Administration and OMCH are working with the Medicaid/Maternal and Child Health Technical Advisory Group in promoting best practices for Medicaid and Title V programs at the state level. In a private/public partnership, the Robert Wood Johnson Foundation and OMCH are collaborating on grant initiatives in states with high infant mortality to support improved health care for pregnant women and their infants.

The prevention of LBW has been identified by the National Institute of Child Health and Human Development as a major research initiative.

A national system that links infant death and birth records is essential to the effective monitoring of trends and identification of high-risk populations. Therefore, a system for matching birth and death certificates has been implemented by NCHS.



Changing Patterns of Groups at High Risk for Hepatitis B in the United States

SINCE 1982, CDC has been conducting intensive surveillance in collaboration with four sentinel counties (Denver County, Colorado; Jefferson County, Alabama; Pierce County, Washington; and Pinellas County, Florida) to determine trends in the epidemiology of acute viral hepatitis in the United States.

1. Hepatitis A (HA)—patient is positive for IgM antibody to hepatitis A virus (IgM anti-HAV).

2. Hepatitis B (HB)—patient is positive for hepatitis B surface antigen (HBsAg) and/or for IgM antibody to hepatitis B core antigen (IgM anti-HBc).

3. Non-A, non-B (NANB) hepatitis—patient is negative for IgM anti-HAV and negative for HBsAg and/or IgM anti-HBc.

From 1982 to 1985, both the overall incidence and the disease transmission patterns of HB were relatively constant. During that time, three major risk factors accounted for almost half of disease transmission: male homosexual activity was reported by an average of 21% of patients; intravenous (IV) drug abuse, by an average of 15%; and heterosexual exposure (sexual contact with a known HB patient, with an HB virus (HBV) carrier, or with multiple partners) was reported by an average of 18%. Other recognized risk factors included health-care employment with frequent blood contact (5%), household contact with a known HB patient or carrier (2%), blood transfusions (2%), dialysis (1%), and residency in an institution for the developmentally disabled (1%). No cases of HB resulting from perinatal transmission were identified in these four counties. For an average of 36% of cases, no source of infection was identified.

Since 1985, although the overall incidence of disease remained stable, IV drug abuse, reported by 27% of patients, replaced homosexual activity as the major risk factor for HBV infection. The proportion of patients whose risk factor for HB was heterosexual exposure (as defined above) also increased to 24%; in contrast, the percentage of patients reporting male homosexual activity declined to 9%, and that of patients reporting healthcare employment with frequent blood contact declined to an average of 1%.

Reported by: WJ Alexander, MD, JG Foster, SB Hill, R Holmes, JFE Shaw, L Wafer, Jefferson County Dept of Health; CH Woernle, MD, State Epidemiologist, Alabama Dept of Public Health, FN Judson, MD, S Minarik, M Shahan, Denver County Dept of Health; RE Hoffman, MD, MPH, State Epidemiologist, Colorado Dept of Health. PY Hu, MD, BR Pixley, Pinellas County Dept of Health; MH Wilder, MD, Acting State Epidemiologist, Florida Dept of Health and Rehabilitative Svcs. AM Allen, MD, E Kramer, A Mares, KA Mottram, C Winegar, Tacoma-Pierce County Dept of Health; JM Kobayashi, MD, State Epidemiologist, Washington Dept of Social and Health Svcs. Hepatitis Br, Div of Viral Diseases, Center for Infectious Diseases, CDC (MMWR vol 37, No. 28).

CDC Editorial Note: The recent changes in the percentage of HB cases attributable to specific groups at high risk for infection are striking. The 57% decrease in the number of HB cases among homosexual men is most likely a result of modification of high-risk sexual behavior to prevent human immunodeficiency virus (HIV) infection. Because the overall incidence rate of HB has remained relatively constant

during this period, the absolute number of HB cases related to drug abuse appears to be increasing, indicating no modification of this high-risk behavior. Although most of the overall increase in IV drug abuse-associated HB found in this study was attributable to one county, similar increases nationwide have been seen in cases of HA, HB, and NANB hepatitis as reported to the National Viral Hepatitis Surveillance Program. These concurrent increases suggest that hepatitis associated with IV drug abuse is a widespread problem (CDC, unpublished data).

It is not surprising that in a sample of this size no perinatal cases of HB were reported. HBV infection in neonates usually results in subclinical infection.

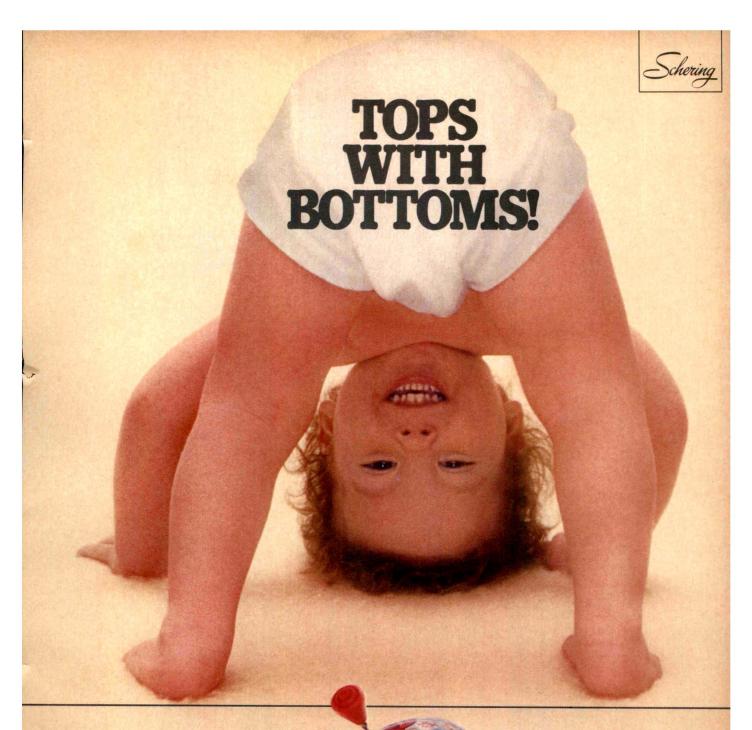
Nationwide, the incidence of HB has increased steadily over the last decade in spite of the availability of a vaccine since 1982. Vaccination programs and vaccine usage have focused primarily on three risk groups—health-care workers who are exposed to blood; staff and residents of institutions for the developmentally disabled; and staff and patients in hemodialysis units. These groups, however, account for only 5%-10% of acute HB cases.

The ability to immunize those groups at highest risk of HBV infection is severely limited for several reasons: the failure of both health-care providers and the target populations to recognize the specific groups at high risk of infection; difficulty in identifying persons with these high-risk behaviors; and difficulties in reaching these groups for delivery of vaccine and in timing of vaccination.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Juvenile Hyaline Fibromatosis: A Histologic and Histochemical Study
Augusto Mayer-da-Silva, MD; Antonio Poiares-Baptista, PhD; Fernando Guerra Rodrigo, PhD; Maria Teresa-Lopes, MD (Arch Pathol Lab Med 1988;112:928-931)



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3. Avoid sources of infection or reinfection.

1. Avoid sources of infection or reinfection.

2. A

Tudage in Pregnancy: Pregnancy Category B: The disposition of 14C-clotimazole has been studied in humans and animals. Clotimazole is very poorly absorbed following dermal application or intravaginal administration to humans. (See CLINICAL PHARMACOLOGY.)

administration to humans. (See CLINICAL PHARMACOLOGY.) In clinical trials, use of vaginally applied clotrimazole in pregnant women in their second and third trimesters has not been associated with ill effects. There are, however, no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. Studies in pregnant rats with intravaginal doses up to 100 mg/kg have revealed no evidence of harm to the fetus due to clotrimazole. High gral doses of clotrimazole in rats and mice ranging from 50 to 120 mg/kg resulted in embryotoxicity (possibly secondary to maternal toxicity), impairment of mating, decreased litter size and number of viable young and decreased pup survival to weaning. However, clotrimazole was not teratogenic in mice, rabbits and rats at oral doses up to 200, 180 and 100 mg/kg, respectively. Oral absorption in the rat amounts to approximately 90% of the administered dose.

Because animal reproduction studies are not always predictive of numan response, this drug should be used only if clearly indicated during the first trimester of pregnancy.

numan responses, mis arrig should be used only it clearly indicated outing the first trimester of pregnancy.

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REFERENCE: 1. Among patients using LOTRIMIN Cream. Spiekermann PH, Young MD: Clinical evaluation of clotrimazole: A broad-spectrum antifungal agent. Arch Dermatol 112:350-352, March 1976.



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Editorial

Unexpected Death in Infants Monitored at Home

Which infants to monitor, for how long, how to decide when monitoring should be discontinued, and how to prevent sudden death in infants for whom home monitoring is recommended: these are controversial questions facing all medical personnel responsible for infants cared for by home monitoring programs. Despite clinical investigations into the causes of infantile apnea and sudden infant death syndrome (SIDS), and despite 15 years of both intervention with home cardiorespiratory monitors and the technological refinement of these machines, there is no definitive proof that the rate of sudden, unexpected infant death has declined. To the contrary, some infants have died despite seemingly adequate efforts to identify those at risk, to intervene with home monitoring, and to instruct caretakers in appropriate cardiopulmonary resuscitation (CPR) maneuvers. 1-3 Yet, no prospective, controlled studies have been published demonstrating that home monitoring has failed to prevent individual sudden infant death or to reduce the rate of SIDS.

See also p 1037.

In a retrospective study in this issue of AJDC, Meny and coworkers4 describe demographic characteristics of ten infants, from a group of 765 highrisk infants monitored at home, who died suddenly and unexpectedly and in whom autopsy findings were consistent with SIDS. Demographic data from 211 other infants who survived in the same group were used for historical comparison. A subset of 42 infants was randomly selected from the "survivor group" to compare factors such as maternal age at the birth of the infant, cigarette smoking exposure during pregnancy, and Apgar scores. Either bronchopulmonary dysplasia (BPD) or severe, apparent lifethreatening events (ALTEs) were diagnosed in six of the ten monitored

infants who died. Other epidemiologic characteristics that statistically separated the survivor and nonsurvivor groups were the lack of private medical insurance, unmarried mother status, and black race. Some of these characteristics have been previously described in studies that focused on risk for SIDS status. 5.6 The most important factor apparently contributing to the deaths was noncompliance with recommended monitoring techniques. However, no historical data on compliance were presented for the survivor group; thus, a comparison of that factor could not be made. Although the comparison group of 211 survivors did not constitute a true control group. the study reports new information and highlights key issues facing home monitoring programs in the efforts to prevent sudden death in their highrisk infants. These issues involve socioeconomic factors predisposing to sudden death those infants who are diagnosed as having ALTE or BPD and for whom monitoring and close follow-up are recommended.

The risks of sudden death in infants with one or more severe ALTEs2,3 or with BPD7 have been previously reported. The diagnoses of BPD and SIDS may be mutually exclusive ones, particularly in those infants discharged with supplemental oxygen for correction of hypoxemia and pulmonary hypertension associated with chronic lung disease. Because of the pathophysiology of the chronic lung disease, infants with BPD have a very high risk of dying unexpectedly. Underlying factors independent of apnea, such as undetected hypoxemia, hypercarbia, and acidosis, can cause progressive pulmonary hypertension. Electrolyte imbalance can cause respiratory control disturbance, and gastroesophageal reflux can cause lung injury from aspiration. In analyzing factors that may contribute to SIDS, we should probably separate deaths in children with BPD from those associated with asymptomatic prematurity

and with ALTE in full-term infants. Apparent life-threatening event is a historical diagnosis,8 and a repeated episode of severe apnea and cyanosis is not often documented during the course of initial hospitalization. Whereas there are no irrefutable data to support the use of home monitoring in ALTE cases, most physicians would monitor an infant whose parents gave a history indicating a need for resuscitation at home; moreover, they would certainly instruct the parents in CPR technique. However, despite the very high risk of sudden death for infants with BPD after discharge from the close scrutiny of a nursery step-down unit, many neonatal units still do not recommend home monitoring for these infants in the absence of documented apnea, even if supplemental home oxygen is required.

If, as Meny and coworkers conclude, improper adherence to monitoring recommendations predisposes an infant to unexpected death at home. follow-up of parental compliance is crucial. However, compliance can only be assessed within a cooperative home setting and with the help of a good home care program. Meny and others3,4 have suggested improving monitors so that they have a time log capacity and can store data of cardiorespiratory patterns around the time of alarm events. In addition, I believe that a good home monitoring intervention program should involve more than simply issuing a monitor and teaching CPR technique. The program should involve a comprehensive approach as follows:

- 1. Adequate clinical and laboratory evaluations should be performed at the time of initial hospitalization to determine need for home monitoring.
- 2. Evaluation of strengths and weaknesses in the family's ability to cope, both financially and psychologically, with the care of an infant who is labeled high risk for sudden death should be performed.
 - 3. Standardized instruction in moni-

tor usage should be conducted so parents understand the pitfalls of monitoring, record the appropriate observations, and respond both to their infant in need and to monitor alarms. Parents should be able to evaluate their infant for respiratory effort, airflow, true central cyanosis, and muscle tone.

- 4. Effective CPR instruction should be given to all caretakers, including day-care personnel, babysitters, relatives, or friends, who may care for the infant in the parents' absence.
- 5. Continued surveillance and input by medical personnel and equipment vendors is needed. By telephone or home visits, they should provide emotional support and continuing instructions and should respond immediately to serious events and equipment malfunction.
- 6. Parental compliance with monitor usage should be time logged, and appropriate methods of feedback

should be planned for parents who do not comply.

Whereas prospective, controlled studies are certainly needed to justify the monitoring of asymptomatic "at risk" infants, I feel that those with histories of ALTE or symptomatic BPD should not only be monitored at home but also be intensively followed up by a home care program such as the one just described. Only then might it be possible to assess the reasons for parental noncompliance and attempt to modify that behavior to reduce the frequency of sudden unexpected deaths in infants monitored at home.

> ROBERT C. BECKERMAN, MD Constance Kaufman Center Department of Pediatrics Tulane University School of Medicine 1430 Tulane Ave New Orleans, LA 70112

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In Other AMA Journals

ARCHIVES OF SURGERY

Required Surgical Therapy in the Pediatric Patient With Dermatomyositis Earl C. Downey, Jr, MD; Morton M. Woolley, MD; Virgil Hanson, MD (Arch Surg 1988;123:1117-1120)

Complications of Prematurity That May Require Surgical Intervention Marshall Z. Schwartz, MD; Steven B. Palder, MD; Kenneth R. T. Tyson, MD; Clifford C. Marr, MD (Arch Surg 1988;123:1135-1138)

The Editorial Board Speaks . . .

Vincent A. Fulginiti, MD





Dr Fulginiti continues as Editor of *AJDC* and is well into his sixth year in that position. He has been a Professor of Pediatrics at the University of Arizona, Tucson, since 1969, and was head of the Department of Pediatrics there for 16 years, from 1969 to 1985. He then joined medical administration as Vice Dean for Academic Affairs and, in 1987, upon the Dean's resignation, became Acting Dean until a new Dean could be appointed.

In May 1988, Dr Fulginiti was awarded the Alumni Achievement Award in Pediatrics by the Alumni Congress of Temple University, Philadelphia. His computerized patient simulations in pediatrics have recently been made available for instructional or evaluative use by medical students and residents and for the continuing education of practitioners.

THE SINGLE PATIENT REPORT

Several years ago, AJDC reversed a long-standing policy and discontinued publication of a large number of single patient reports (many call these "case" reports, but this term is too dehumanizing, and is not used by AJDC). We did so because most of these were of the "me too," or "nth instance of . . ." type. We did not feel that such contributions were useful to our readers, nor were they important enough to occupy valuable editorial space. We still do publish patient reports, either as full original articles, when they are unique, or as a pediatric forum submission when they are valuable reminders of an important point in the care of children.

Since this change in policy we have had multiple conversations and letters concerning the value of patient reports and we continue to receive some 100 such reports each year (we sincerely believe that authors do not read the instructions, and possibly the journal!), a very few of which ultimately find a place in AJDC. We do not intend to denigrate the value or the need for careful clinical observation. Many on our editorial board have made such critical observations, which stimulated them or others to probe more deeply and to uncover some basic biologic principle or to widen our knowledge in some other way. But these observations were seminal in nature, not repetitions of what was well known or repeatedly observed. For example, many of our submissions begin with, "The authors report the nth patient with [disease x]," or "Although Smith and Jones described 40 patients with this disorder in 1978, we describe an additional patient because it has been so long. . . ."

Seminal observations have the quality of reporting something that no one has noted before or contradicting, expanding, or otherwise altering, in a major way, established clinical or scientific dogma. There are some observations that clinicians make that serve to point out a new danger to children ("Foreign Body Aspiration," AJDC 1988;142:485-486), to alert us to a clinical condition we might otherwise miss ("Vitamin K Prophylaxis: Oral or Parenteral?" AJDC 1988;142:14-15), to update us on drug toxicity not thought to occur in children ("Naproxen Nephrotoxicity in a 2-Year-Old Child," AJDC 1988;142:524-525), or to suggest a new diagnostic or therapeutic approach ("Achalasia in Children," AJDC 1988;142:16). I selected these recent examples to illustrate how our current policy

works in practice.

All of us appreciate the need for clinical observation, hence the patient report. Who can deny the value of Dr Bruton's description of the first patient identified as being gamma globulin-deficient? But, as that patient report illustrates, a further value of the clinical observation is the ability to ask the right questions and to carry them into the laboratory to obtain the answers. This type of patient report is the most valuable and completes the empiric observation-to-research cycle.

There is yet another type of patient report that is often the most difficult of all to judge. This is the report that observes a "new" syndrome, clinical disorder, or concurrent occurrence of two seemingly unrelated disorders, or associates a clinical finding with a given laboratory or radiologic observation. Each of these have in common a potentially unique observation that may be "landmark" or may be totally wrong. The "new" syndrome may be one already reported or mistaken for a more common one; the new clinical disorder may just be careless description or a variant of a known condition; the concurrence of two conditions may be simply temporal association by chance; and the laboratory or radiologic finding may be totally disconnected with the clinical observation. On the other hand, the new syndrome may be fetal alcohol syndrome; the new clinical disorder may be Kawasaki or Lyme disease; the concurrence may be aspirin and Reye's syndrome; and the link between the laboratory and clinical observation may be hypogammaglobulinemia. The editor is truly in a dilemma when judging the suitability of such observations for publication in his or her journal. Some have suggested a special section devoted to "speculative clinical observations." The problem with that solution is that computerseeking probes will not necessarily identify the article as speculative, lending its words a credence they may not deserve.

We will continue to struggle with the single patient report; we will probably reject some that are truly worthwhile, even significant observations. We will accept and publish some that are incorrect or inadequate observations. However, we can only rely on our referees', Editorial Board members', and, ultimately, the Editor's judgment . . . the decision is that frail!

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Sudden Infant Death and Home Monitors

Robert G. Meny, MD; Lillian Blackmon, MD; Deborah Fleischmann, BSN; Ronald Gutberlet, MD; Eric Naumburg, MD

 During a two-year period, ten infants died suddenly and unexpectedly with a home cardiorespiratory monitor available. We investigated the compliance with appropriate monitoring technique as well as the medical and demographic factors associated with these deaths (90% were due to sudden infant death syndrome). At least six and probably eight of these ten families were noncompliant with appropriate monitoring technique. The main comparison group consisted of 211 patients for whom care with home cardiorespiratory monitors was initiated and continued. Bronchopulmonary dysplasia and severe, apparent life-threatening events were significantly increased in the subjects, as were the following characteristics: black race; lack of private medical insurance; unmarried mother; maternal age of less than 25 years; cigarette smoking by mother during pregnancy; and low Apgar scores. These diagnostic and demographic factors may be useful in predicting the infant at highest risk for sudden and unexpected death when a home monitor is prescribed. Noncompliance with proper monitoring technique occurred in a majority of the study patients; methods of educating parents of infants at high risk of sudden infant death syndrome with the necessity for compliance need to be developed.

(AJDC 1988;142:1037-1040)

During 1985 we noted a marked increase in sudden and unexpected deaths in infants at high risk of sudden infant death syndrome (SIDS) for

For editorial comment see p 1033.

whom home cardiorespiratory monitors had been prescribed and initiated. We therefore retrospectively investigated the factors associated with these eight deaths and two others that had occurred the previous year. Special attention was given to the pattern of monitor use or nonuse at the time of death, to the initial reasons for recommending monitoring, and to familial demographic characteristics. To our knowledge, this is the first article from a single center that examines in detail the circumstances surrounding such deaths.

PATIENTS AND METHODS

The study group consisted of ten infants who died suddenly and unexpectedly between Dec 7, 1983, and Dec 9, 1985, despite the availability of a home cardiorespiratory monitor that had been prescribed for their condition. During this period, care with a home monitor had been initiated for 765 infants; approximately 120 infants were followed at any given time.

Table 1 supplies demographic and medical data on these ten infants, five of whom were born prematurely. The lack of private medical insurance is used as an indicator of lower socioeconomic status. Patient 3 was the sole infant whose parents had private medical insurance, and only two patients had parents who were married.

A severe, apparent life-threatening event (ALTE) was defined as an episode that is frightening to the observer and that is characterized by some combination of apnea, color change, marked change in muscle tone, choking or gagging, and need for mouth-to-mouth resuscitation or vigorous stimulation.

Bronchopulmonary dysplasia (BPD) was diagnosed by the need for supplemental oxygen beyond 30 days of age and typical roentgenograms. Two of these infants had BPD of sufficient severity to warrant home oxygen therapy. However, these two infants showed marked clinical improvement before death with oxygen therapy discontinued in one case and tapered in the other case. In addition, both patients were gaining weight before death.

Nine infants were evaluated with daytime polysomnography and a feeding study.² Further workup of the ten infants was individualized according to their diagnosis and symptoms, if any.

Impedance-type monitors with apnea delay set at 20 s and the bradycardia alarm set according to age were prescribed for the infants. The monitors were to be used during sleep and when the infants were unattended. Monitor company personnel taught monitor use to parents.

The staff at The SIDS Institute, Baltimore, taught two family members or friends cardiopulmonary resuscitation (CPR) and a graded response to a monitor alarm. This response consisted of observation for 5 s before intervention unless the infant exhibited a color change. Intervention consisted of gentle stimulation followed by vigorous stimulation and then CPR if needed. Staff members and monitor company personnel were available on a 24-hour basis.

After learning of a death, we contacted the family to express our sorrow and to discuss the infant's health in the days before death. The details of when the infant was discovered, the type of alarm and its duration, and the resuscitative measures undertaken were discussed. Our prior contacts with the family members and others involved in the infant's care were reviewed as well.

Questionable use of the monitor was defined as conflicting histories of monitor use or circumstantial evidence of noncompliance at the time of death plus a history of previous noncompliance using the monitor. Nonuse defined as the admission by the parent or family members that the monitor was not in use at the time of death.

A comparison group for medical and demographic factors consisted of 211 new patients, seen at the SIDS clinic in the first half of 1985, who survived with the assistance of a home cardiorespiratory monitor. To compare maternal age at birth of the infant, use of cigarettes during pregnancy, and Apgar scores between the infants who died and the survivors, a subset of 42 patients was selected at random from the larger comparison group. A special effort was made to ascertain this information retrospectively since it was not routinely collected for all patients. None of the 211 infants is known to have died of SIDS

Accepted for publication July 14, 1988.

From the Department of Pediatrics, University of Maryland School of Medicine, Baltimore, and The SIDS Institute, University of Maryland Hospital, Baltimore.

Reprint requests to The SIDS Institute, Room N5W67, University of Maryland Hospital, 22 S Greene St, Baltimore, MD 21201 (Dr Meny).

| Patient No. | Birth Weight, g/ Gestational Age, wk | Race/Sex | Maternal Age at Birth, y | Indication for Monitor | Age at Death, mo | Monitor in Use or Properly Used | | |
|----------------|---|----------|-----------------------------|--|---------------------|------------------------------------|--|--|
| 1 | 840/25 | B/M | 20 | Mild BPD, AP | 6 | No | | |
| 2 | 960/27 | W/M | 19 | BPD requiring home oxygen, AP | 4 | No | | |
| 3 | 1280/28 | W/M | 29 | BPD requiring home oxygen, AP | 5 | No | | |
| 4 | 1200/29 | B/M | 23 | AP, abnormal PS results | 6 | Questionable use | | |
| 5 | 1670/31 | B/M | 24 | Heroin withdrawal, abnormal PS results | 4 | No | | |
| 6 | 3060/40 | W/F | 21 | Severe ALTE | 3 | No | | |
| 7 | 3420/40 | B/F | 17 | Severe ALTE | 10 | Yes | | |
| 8 | 3400/40 | B/M | 21 | Severe ALTE, half-sibling of SIDS victim | 2 | Yes | | |
| 9 | 3345/39 | B/M | 21 | Half-sibling of two SIDS victims | 4 | Improper use | | |
| 10 | 3780/41 | B/M | 24 | Half-sibling of SIDS victim | 2 | Questionable use | | |

*BPD indicates bronchopulmonary dysplasia; AP, apnea of prematurity; ALTE, apparent life-threatening event; SIDS, sudden infant death syndrome; and PS, polygraphic studies.

| | 100 | Table 2 | 2.—Interaction With Families* | | |
|----------------|--|-------------------------------|--|---|--------------------------|
| Patient No. | Days From Initiation of Home Monitoring to Death | SIDS and BPD Clinic Visits | Home Visits by Medical and Monitor Company Personnel | Calls and Letters From Monitor Company and SIDS and BPD Clinics | Total Actual Contacts |
| 1 | 14 | 2 | 18† | 0 | 20 |
| 2 | 27 | 3 | 6 ± | 0 | 9 |
| 3 | 73 | 4 | 3 | 1 | 8 |
| 4 | 31 | 2 | 10 | 6 | 18 |
| 5 | 105 | 1 | 2= | 5 | 8 |
| 6 | 26 | 1 | 2 | 2 | 5 |
| 7 | 17 | 1 | 1 | 1 | 3 |
| 8 | 9 | 3 | 1 | 3 | 7 |
| 9 | 111 | 2 | 1 | 5 | 8 |
| 10 | 72 | 1 | 4 | 2 | 7 |

^{*}SIDS indicates sudden infant death syndrome; BPD, bronchopulmonary dysplasia.

following discontinuation of home monitor-

Autopsies were performed at the Office of the Medical Examiner in Baltimore following a standard protocol. Autopsy reports and medical examiner's investigation reports were reviewed with special attention for known causes of death, including trauma.

Statistical significance of demographic and medical risk factors was assessed with Fisher's exact test, one-tailed, when the a priori assumption was made that these risk factors for SIDS would be increased in the study patients. Otherwise, the two-tailed Fisher's test was used. In all cases a P value of less than .05 was taken as a rejection of the null hypothesis.

This study was approved by the Human Volunteers Research Committee at the University of Maryland Hospital, Baltimore.

RESULTS **Autopsy Findings**

Findings in all nine autopsies were compatible with SIDS. The pulmonary

pathologic conditions present in two of the infants with BPD were not sufficient to cause death, an impression supported by the relatively benign clinical courses before death. One infant with BPD died suddenly and unexpectedly but could not be classified as a SIDS victim because an autopsy was not performed.

Compliance

The rate of noncompliance was at least 60% and was probably 80%. Five infants were not attached to their prescribed monitors at the time of death. Improper monitoring technique was used for one other patient (patient 9). Two infants were apparently properly monitored at the time of their death. Monitor use was questionable for two other infants (patients

The reason for nonuse of the monitor was elicited for four infants. The mother of patient 1 had fed him while he was unattached to the monitor. He remained unattached after he had finished his meal and died while his mother slept. The monitor attached to patient 2 was turned off after several alarms, which were judged to have been false by his parent. Patient 3 died during a daytime nap; his parents believed that he needed to be on the monitor only at night. The parents of patient 6 separated; the infant was taken to a relative's house but her monitor was left behind.

The alarm sounded on patient 9's monitor, but the amount of time that had passed before it was heard is unknown because the father had left the child unattended in the house. Sometime after his return he heard the alarm. His ability to hear it was probably impaired as a television was on in the infant's upstairs bedroom and the father was downstairs. When he

fincludes visits by home health aide

[‡]Includes visits by Protective Services personnel.

reached the infant, there was no cardiac or respiratory activity and CPR did not elicit any response.

The parent of patient 4 stated that the monitor was in use but contradicted herself on the occurrence of an alarm at the time of death. Paramedics who attempted CPR at the infant's home did not see the monitor. Furthermore, a public health nurse during an earlier home visit noted that the sleeping infant was unmonitored.

Monitor company personnel and a public health nurse noted that patient 10 was not being monitored during several home visits. When the device was retrieved three days after death, it and, specifically, its on-off switch were covered by dust and cobwebs. Nevertheless, the mother insisted that the infant was monitored at the time of death.

Table 2 portrays the follow-up provided by various persons involved in the care of these infants. Contact began a few days before the initiation of home monitoring or initial SIDS clinic evaluation, whichever came first. Five of ten infants survived for less than one month after the initiation of home monitoring, including all three of the infants presenting with a severe ALTE. The two infants (patients 1 and 4) with the largest number of contacts had relatively short survivals after home monitoring was initiated. Patient 5 had three times as many attempted home visits as actual ones; his mother frequently moved without notifying Protective Services personnel and the others involved in this infant's care.

Diagnostic and Demographic Data

The diagnoses of BPD (30% of study group vs 7.6% of comparison group) and severe ALTE (30% vs 6.6%) were both associated with an increased risk of sudden and unexpected death with a home monitor available. The demographic factors of race (black: 70% of study group vs 34% of comparison group), lack of private medical insurance (90% vs 52%), maternal age of less than 25 years (90% vs 50%), and unmarried mothers (80% vs 43%), several of which are indicators of poverty, were similarly associated with death (P<.05). Cigarette use during preg-

nancy and low Apgar scores were also significantly associated with these deaths.

During home monitoring, infants who had severe ALTEs causing intervention or whose alarms sounded, resulting in hospitalization, may have survived because of good compliance followed by successful resuscitation or the appropriate decision to have the infant evaluated. There were 17 such infants (15 infants with ALTE and two infants hospitalized) out of 211 infants who may therefore be the survivors who best approximate our study patients save for compliance at a critical time and/or successful resuscitation. Comparison with the study patients shows that black race (P = .007), lack of Medicaid or private insurance (P=.062), unmarried mother status (P = .013), Apgar scores of less than 7 at one minute (P = .028) and less than 4 at one minute (P = .085) all remain overrepresented in the study group (Fisher's two-tailed exact test).

COMMENT

The finding that up to eight of the ten deaths were associated with noncompliance or improper monitor use is quite disturbing. It is, however, in accord with the findings of Davidson-Ward et al,3 who reported that of seven SIDS victims for whom monitoring was recommended, five deaths (71%) were associated with noncompliance or technical errors in monitor use. Although this behavior follows false monitor alarms in some cases, and the demographics are consistent with poor, single-parent households where monitoring could be a substantial burden, it is clear that more effort is needed to discover the causes of noncompliance. This effort was in fact recently advocated by the National Institutes of Health Consensus Development Conference.1

A limitation of this study is that systematic, detailed investigation of compliance was limited to the time of death; therefore, several families labeled as "noncompliant" may actually have been compliant most of the time. Conversely, it is possible that many survivors were not monitored appropriately. Furthermore, the absence of meaningful alarms in the majority of

the comparison infants could imply that compliance status was irrelevant to their survival. We chose not to investigate compliance retrospectively because the passage of several years would perhaps lessen the accuracy of responses and further questioning could cause distress to the patients' families.

Infants with BPD accounted for 30% of these deaths, but only 7.6% of our comparison infants had this diagnosis. This finding agrees with that of Werthammer et al,4 who showed that infants with this diagnosis were at a sevenfold increase in risk for SIDS compared with premature infants with birth weights of less than 1.0 kg but free of BPD. Sauve and Singhal⁵ also noted a much higher mortality for infants with BPD, although only one of the 12 infants who underwent autopsy was a victim of SIDS while chronic lung disease was the cause of death for the majority. These two articles illustrate not only that the risk of sudden death is increased with this diagnosis, but that the stated cause of death. SIDS vs chronic lung disease. may reflect differing interpretations of histopathologic findings and prior clinical course. Whatever the label, all three of these infants died unmonitored following an improving clinical course in the weeks before death. Although the use of a monitor is not a guarantee against death, we do feel that attention to proper monitor use is reasonable to encourage these infants.

The other major risk group consisted of the three patients with a severe ALTE (near-misses). Oren et al⁶ stated that following an ALTE requiring resuscitation, all infants having further episodes experienced them within two weeks of hospital discharge. Our infants with an ALTE were similar in that death occurred within four weeks of initiation of home monitoring.

Sudden infant death syndrome is increased in male infants, ^{7,8} black infants, ⁹ and infants of young mothers ^{7,8} who are poor. ¹⁰ Our infants were similar to SIDS victims in general: 80% of our infants were male and 70% were black. Nine of ten patients were without private medical insurance, indicating that most of these infants came

from impoverished homes, an impression that is strengthened by the fact that 80% of the mothers were unmarried and 90% were less than 25 years old. Low Apgar scores^{8,11} and cigarette use during pregnancy^{8,11} have also been associated with increased risk for SIDS and hold true for our study group.

The possibility that home monitoring may be associated with increased risk for child abuse has been raised.1 Indeed, Davidson-Ward et al,3 in their study of sudden and unexpected death after evaluation by apnea programs, found that four of 26 infants died of "nonaccidental trauma," but only one of these homicides occurred in the subgroup of ten infants who had monitoring recommended at the time of death. None of our patients had evidence of blunt trauma on autopsy (n=9) or external examination only (n=1). Since blunt trauma was the most frequent method of homicide of

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 Sauve RS, Singhal N: Long-term morbidity of infants with bronchopulmonary dysplasia. Pediatrics 1985;76:725-733. infants in Erie County, New York, 12 and of children 0 to 4 years of age in Cuyahoga County, Ohio, 13 this lack of blunt trauma in our patients is somewhat reassuring that homicide did not occur. Further reassurance is supplied in the description by Rosen et al 14 of patients who present with apnea requiring resuscitation but who in fact are victims of child abuse—Munchhausen's syndrome by proxy. The three patients with a severe ALTE did not have histories suggestive of this syndrome.

We suggest that any evaluation of the efficacy of home cardiorespiratory monitoring for the prevention of SIDS or other forms of death should take into account the poor compliance rate noted in this and other studies. Future assessment of home monitoring efficacy would, therefore, be aided by adding time meters to measure the actual use of the home monitor and a recorder with a continually updated

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memory to capture the events up to and including death. Indeed, the ideal apnea monitor has been characterized as having a data storage system.15 In summary, there was a high percentage of noncompliance with appropriate monitoring technique by the families of these ten patients, nine of whom were SIDS victims. The diagnoses of BPD and severe ALTE were significantly increased in these infants, as were demographic factors of which some are associated with lower socioeconomic status. Compliance may be aided by improving home monitors and by learning how to best educate families in the proper use of these devices. More research is needed to determine reasons for noncompliance and ways to lessen it with the hope this will lead to a reduction in mortality.

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In Other AMA Journals

ARCHIVES OF SURGERY

Diagnostic and Surgical Implications of Child Abuse

Daniel J. Ledbetter, MD; Edwin I. Hatch, Jr, MD; Kenneth W. Feldman, MD; Corinne L. Fligner, MD; David Tapper, MD (Arch Surg 1988;123:1101-1105)

Respiratory Failure From Asthma

A Marker for Children With High Morbidity and Mortality

Richard W. Newcomb, MD, Javeed Akhter, MD

 During a seven-year interval, 78 children had documented episodes of respiratory failure from asthma, defined as arterial hypoxemia, hypercapnia, or use of mechanical ventilatory support or intravenous isoproterenol hydrochloride. During 407 patient-years of follow-up (5.2 years per patient), these 78 children had 227 episodes of respiratory failure (2.9 episodes per patient). Fifty-three patients (68%) have had two or more of such episodes. Second episodes usually followed the initial episodes within two years, but some were delayed for over six years. Seven of the 78 children died, and two others have incurred hypoxic brain damage, compared with two deaths among 2892 children with asthma—seen at this hospital during that interval-but without a documented previous episode of respiratory failure. We conclude that children whose asthma has caused even one episode of respiratory failure constitute a special group of asthmatic patients, members of which are at high risk for repeated episodes of respiratory failure and its catastrophic complications. This recognition allows special attention to be focused on them in designing both clinical and research strategies.

(AJDC 1988;142:1041-1044)

Most episodes of asthma, even those requiring hospital care for "status asthmaticus," do not involve respiratory failure. As airway obstruction increases during an episode of asthma, arterial blood gas values progress through a characteristic series of stages. 1,2 Both arterial oxygen tension (Pao₂) and carbon dioxide tension (Paco₂) decrease early, but oxygen saturation of hemoglobin is less affected by changes in a Pao₂ above 50 mm Hg than below that value, which thus delineates serious hypoxemia. A rise of Paco₂ from its depressed

levels into the "normal" range and beyond signifies further deterioration. Respiratory failure with hypoxemia alone is thus distinguished from respiratory failure with hypoxemia and carbon dioxide retention³ (sometimes called type I and type II respiratory failure).

It is thought that most deaths from asthma follow respiratory failure that has been untreated or undertreated owing to lack of appreciation of its severity by patients or physicians.4 Nonlethal brain damage from asthma may have the same pathogenesis.5 These catastrophes, however, are rare, and treating all patients as if they were in equal danger of respiratory failure from asthma would unnecessarily strain medical resources. Therefore, a simple means of identifying patients at risk of this complication would allow attention to be focused on those most in need.

In studies concerning outcomes of the emergency room (ER) care of asthma,6.7 we have noted that nearly all episodes of very severe asthma involved members of a previously selected "high-risk" group, amounting to about 8% of children then under treatment for asthma at La Rabida Children's Hospital (LRCH), Chicago. This group had been selected for this study for a variety of reasons, but usually for having previous severe episodes of asthma, including respiratory failure. We hypothesize the existence of a distinct prognostic category of children who run a high risk that asthma will result in respiratory failure and its consequences, and that this group can be identified from a history of asthma leading to at least one episode of respiratory failure. We describe herein evidence supporting this hypothesis.

PATIENTS AND METHODS Patients and Setting

La Rabida Children's Hospital is a specialty hospital staffed by University of Chicago pediatric faculty and residents. The management of asthma at LRCH has been previously described.*.

From 1979 through 1984, 2970 children (boys vs girls, 58% vs 42%) with asthma were seen at LRCH. Most patients were black residents of the neighboring southeast and south central sectors of Chicago; nearly all patients were drawn from these areas and adjacent communities in Illinois and Indiana containing a population of approximately 1.5 million and served by many other hospitals.

For purposes of this study, respiratory failure was diagnosed if arterial blood, drawn after at least two doses of sympathomimetic bronchodilators were administered in the ER or hospital, had a Pao. of less than 50 mm Hg or a Paco₂ of greater than 45 mm Hg. For patients receiving supplemental oxygen at a known level, the diagnosis was also accepted if the arterialalveolar oxygen tension ratio (Pao₂/PAo₂) calculated from the alveolar gas equations was less than 0.50. If qualifying blood gas data were not available from other institutions, the diagnosis was accepted if the patient had received treatment for asthma with intravenous isoproterenol hydrochloride; had been intubated and ventilated for asthma; or, as in one case, had experienced asthma culminating in cyanosis and a seizure responsive to treatment for asthma without anticonvulsant therapy, when the plasma theophylline level was less than 28 μmol/L.

Patient Selection

The study group was selected to include all those patients who had at least one documented episode of respiratory failure caused by asthma from January 1979 through December 1984. Names were obtained from the original 1983 "High-Risk" list, compiled to guide ER management. Additional names were sought in the logs of ER transfers to the intensive care unit, admissions list of the intensive care unit, and log of the blood gas laboratory from 1979 through 1984.

Twelve of the 90 patients from the "High-Risk" list were excluded because their records failed to meet the study criteria for respiratory failure. Four more patients were excluded because reasons other than asthma were found for their respiratory

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Reprint requests to 8683 Connecticut Ave, Merrillville, IN 46410 (Dr Newcomb). failures (one had a poliolike disorder, two had subglottic stenosis, and one had been intubated when her asthmatic cough was diagnosed as epiglottitis). We added four patients not on the original list but who had respiratory failure from asthma between 1979 and 1984.

Data Collection

The records at LRCH for all patients were available and complete, but records from other hospitals were often unavailable. Beginning in 1984, we retrospectively examined all available records and collected data according to predetermined criteria. From 1984 through 1986, data collection was prospective. Data constituted demographic descriptors, disease descriptions, and details of each episode of respiratory failure. (Specific criteria will be supplied on request.)

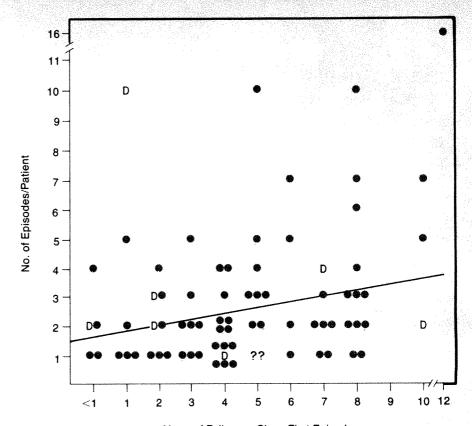
Statistical Methods

Group differences were compared by uncorrected χ^2 analysis. A P value of less than .05 was considered to be significant. Regression was estimated by the least squares method.

RESULTS

Seventy-eight patients had 197 documented episodes of respiratory failure from asthma by the end of 1984 and 30 additional episodes by the end of 1986. Twenty-three of 197 episodes occurred at other institutions. The 174 episodes at LRCH constituted 3.7% of all 4700 admissions for asthma from 1979 through 1984. The 78 children constituted 2.6% of the 2970 patients with asthma seen in that interval and approximately 8% of the 824 to 923 patients who were "active" in any given year (those who made at least one hospital visit in that year).

Demographic characteristics and neighborhoods of residence failed to distinguish the 78 patients with respiratory failure from the population of asthmatic children as a whole. Of the 78 patients, 44 (57%) were boys and 70 (90%) lived in Chicago's southeast and south central sectors. They also resembled most of our patients in that 58 children (78%) either received state medical aid or were without medical financial resources. At the time of their first episode of respiratory failure, their mean age was 7.1 years (range, 7 months to 18 years 8 months). Maintenance therapy with oral corticosteroids (usually alternateday administration of prednisone) had



Years of Follow-up Since First Episode

Fig 1.—Patients with respiratory failure from asthma (n=78) identified according to years of follow-up since their first episode of failure and number of episodes of respiratory failure. Solid circles indicate survivors; Ds, deceased patients; and ?s, those whose follow-up was unsatisfactory. Regression line was estimated by least squares method.

been used at some time for 45 patients (58%). Compliance was noted as a problem in the medical records of 29 patients (37%).

We have followed up the 78 patients for a total of 407 patient-years (5.2 years per patient; range, one month to 12 years), during which 53 patients (68%) had at least one recurrence of respiratory failure (Fig 1). The number of episodes per patient has tended to rise with length of follow-up, although the trend is weak (r=.27).

When respiratory failure recurred it did so usually soon after the first episode. We have accurate dates for the initial and second failures in 50 patients (Fig 2), and in 23 (46%) of these cases, respiratory failure recurred within six months; in 38 cases (76%), it recurred within two years. Among the 28 patients who had three or more episodes of respiratory failure, the interval between the first and third episodes was less than two years in 15 cases (53%). A long interval free of recurrences of respiratory failure

did not necessarily afford a margin of safety: over six years elapsed from the first to the second failures in four patients, one of whom subsequently died, while another patient sustained hypoxic brain damage during an episode of asthma.

The diagnosis of respiratory failure rested on manifestations that ranged from hypoxemia to carbon dioxide retention and cardiopulmonary arrest. Hypoxemia alone on the initial episode carried a slightly lower chance that respiratory failure would recur than did more severe initial episodes. In 32 patients for whom hypoxemia was the only criterion on the initial respiratory failure, 17 patients (53%) have had recurrences, compared with a 76% recurrence rate among the 42 patients who had more severe initial episodes (.05>P>.025). It did not matter (P>.10) whether the hypoxemia had been diagnosed from a Pao₂ value of less than 50 mm Hg or a Pao₂-PAo₂ ratio of less than 0.50.

Seven of the 78 patients died of

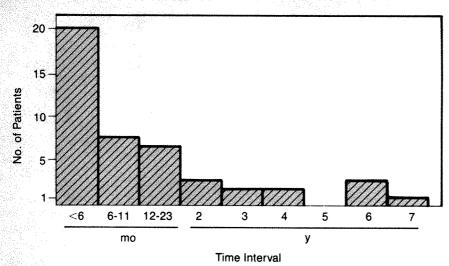


Fig 2.—Number of intervals between first and second episodes of respiratory failure from asthma for 50 patients with at least two documented episodes.

asthma during 407 patient-years of follow-up. Among 2892 patients without a prior history of respiratory failure, followed up for an estimated 5900 patient-years, two patients died of asthma. The case fatality rate of asthma in the 78 patients was therefore 1720 deaths per $100\,000$ patient-years of follow-up, compared with 143 deaths (nine deaths per 6307 patient-years) for our total population (P<.0005) and 34 deaths per $100\,000$ patient-years for those with no preceding respiratory failure.

In addition, two of 78 patients have suffered severe brain damage, leading to blindness in one patient and visual aphasia, hypermetamorphosis, shortterm memory loss, and behavioral changes (Klüver-Bucy syndrome)10 in the other patient. Seven others have had convulsions during asthma attacks that were not part of a seizure disorder or theophylline toxicity.5 The nine patients who died or suffered severe brain damage had more severe initial and recurrent episodes of respiratory failure, not including the catastrophic episodes themselves, than the other 65 children with adequate data (details of the level of severity were lacking for initial or recurrent episodes in four of 69 patients). On their initial episodes, eight of the nine patients retained carbon dioxide and two patients received mechanical ventilatory support. Moreover, 23 (79%) of their total 29 precatastrophe episodes involved carbon dioxide retention, intravenous isoproterenol, or mechanical ventilatory support. Only one deceased patient failed to have at least one prior episode of carbon dioxide retention. By contrast, hypoxemia was the only diagnostic criterion for 75 (48%) of the 156 episodes in the 65 catastrophe-free children (P<.01), 31 (48%) of whom never retained carbon dioxide (.5>P>.025).

COMMENT

The ability to distinguish prognostic categories among patients with a single diagnosis is essential for competent performance of clinical studies and for planning effective clinical strategies.11 Among children with asthma, a number of dimensions of the disease may be used for classification. Most common has been "severity," but there is no uniform method by which severity is gauged. Different authors have used frequency of symptoms, 12,13 persistence of pulmonary function abnormalities,14,15 degree of disability (eg, days of school lost, 16 growth failure, or chest deformity¹⁷), or level of medical intervention (frequency of ER visits, hospital admissions, 18 and patof terns drug use, especially steroids19).

We reasoned that the danger of having the disease is in fact related to the maximum severity of asthma episodes. We hypothesized the existence of a distinct prognostic category of patients with high susceptibility to severe asthma episodes. As objective evidence of severity, we chose documented episodes of respiratory failure.

Data presented herein confirm our hypothesis. From a large population of children with asthma, we identified 78 patients with a history of respiratory failure from asthma, 53 of whom had recurrent respiratory failures and nine of whom incurred brain damage or death during asthma episodes. A further substratification among the 78 patients was suggested by the fact that those whose initial episodes of respiratory failure included both hypoxemia and carbon dioxide retention were significantly more likely to have recurrences of respiratory failure and to suffer brain damage or death than patients whose initial episodes involved only hypoxemia.

Our patients were drawn from a population of predominantly innercity, black children, most of whom had been hospitalized for asthma at some time. Such a population would be expected to have relatively high mortality from asthma compared with other American children with asthma. Nevertheless, the risk of death in our population was concentrated in the 8% with a history of respiratory failure; those without such a history appeared to run a far lesser risk from asthma.

The existence of a stratum of asthmatic children at high risk of respiratory failure and its complications has been repeatedly suggested but never before clearly established. The adults and children selected for an "emergency admission list" by Crompton et al21 were chosen for having had previous "severe status asthmaticus" without other stated criteria. They have also had high rates of recurrent respiratory failure and deaths. We limited our group to those with objectively documented respiratory failure. This approach was justified by the needs of our study but, in the practice of clinical medicine, incomplete medical records might exclude truly high-risk asthmatic patients. Therefore, it would be wise to assume that all patients with unusually severe asthma episodes deserve special consideration. Our recent experience emphasizes this lesson: Since the end of 1986, asthma has proven fatal to two of the 12 children on our original "High-Risk" list but not included in this study for lack of documentation that their clinically severe episodes

entailed respiratory failure (J.A., unpublished data, 1987).

Reports of deaths from asthma have also indicated that fatal cases had been drawn from a special group of patients. but a comprehensive view of such a group has never emerged. Most patients dying of asthma have had previous severe episodes.22,23 Moreover, survivors of mechanical ventilatory support for asthma were found to have high rates of recurrence and death.24.25 Although this relationship was not found in one case-control study of fatal asthma,2 expanded follow-up by the same group²⁶ has indicated a significant relationship between death from asthma and a history of "respiratory failure requiring mechanical ventilation." This criterion will select only a fraction of patients with respiratory failure: 62 (79%) of our 78 patients and seven of the nine who eventually died or had brain damage had never previously received mechanical ventilatory support.

A recent task force report on asthma mortality²⁷ has identified two groups at risk of dying of asthma: the first group with "a history of a near-death episode requiring resuscitation" and the second group with "severe" disease, characterized in part

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by "respiratory failure requiring ventilation or isoproterenol infusion, or history of a hypoxic seizure accompanying an asthma attack" plus a complex of psychosocial attributes. Our data suggest that most children who die of asthma are drawn from a more simply defined group comprising those with previous respiratory failure from asthma based on blood gas criteria. Behavioral and psychological attributes may indeed differentiate high-risk patients who die from those who survive, 19,23,26 but psychosocial problems are common in children with debilitating asthma and may represent a risk factor only in patients who are also susceptible to respiratory failure for basic, pathophysiologic reasons.

It is unknown what pathophysiologic conditions distinguish asthma that results in repeated respiratory failure. Better understanding might allow such patients to be treated more effectively and even identified before their first respiratory failure (fortunately, few initial episodes have been fatal). Further studies of this population are planned to investigate the many unanswered questions about children whose asthma results in respiratory failure.

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We have no proven way to manage patients after an episode of respiratory failure from asthma, but we generally follow the suggestions of others for patients who are at high-risk of fatal asthma.28 The parents and also the patients are advised of the dangerous nature of the disease, and they receive a note outlining the patient's individual problems and guidelines for emergency care. The note specifies an individual treatment plan for increased symptoms, expected response in terms of objective measurements (usually peak flow rates), and conservative criteria for hospital admission. Peak flowmeters are dispensed to most patients. Copies of the notes are given to the parents and to appropriate ERs. Direct telephone access to senior physicians is provided, including home and telepager numbers. Attention is given to educating and encouraging full, age-appropriate activities and participation of the children in their own care. More work is needed to determine whether any of these efforts prevent recurrences of respiratory failure or its catastrophic consequences.

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Clinical Predictors of Severe Head Trauma in Children

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· We reviewed the medical records of 55 patients who underwent a cranial computed tomographic (CT) scan for acute head trauma. The severity of head trauma was classified according to objective clinical findings as severe in 44 patients, moderate in three, and mild in eight. Thirty-seven patients (84%) with severe head trauma had a brain injury identified on CT scan. Six patients with severe head trauma had a Glasgow Coma Scale score of 12 or greater and an abnormal CT scan. All patients with mild or moderate head trauma had normal CT scans. Severe head trauma, as defined in this study, accurately identified all patients with abnormal CT scan findings. We conclude that a classification based on objective clinical findings accurately identifies the severity of head trauma. This is particularly important in evaluating patients with a Glasgow Coma Scale score of 12 or greater. A prospective study including larger numbers of patients is needed to further evaluate such a classification.

(AJDC 1988;142:1045-1047)

Accidents account for approximately 50% of all deaths in children aged 1 through 14 years in the United States. Almost 80% of all pediatric patients with multiple trauma have an associated head injury. 12 Head trauma accounts for approximately 250 000 admissions and 600 000 emergency department visits annually, with 6% to 30% morbidity. 1-6

Early diagnosis of the nature and extent of intracranial injury and aggressive medical or surgical management results in significant reduction of mortality and morbidity.^{2,3} To initiate appropriate care, emergency department physicians caring for acutely injured children need to rapidly and accurately identify patients with severe head trauma and brain injury.

Cranial computed tomographic (CT) scan provides a safe and accurate means to identify and evaluate the nature and extent of intracranial injury. The emergency department physician needs clinical variables that have been shown to be predictive of intracranial injury.

The introduction of the Glasgow Coma Scale (GCS) in 1977 resulted in marked improvement in the management of head trauma.7 This has aided the clinician in determining the appropriate modes of patient monitoring, detecting complications early, planning therapy, and comparing the severity of injury in different patients. Raimondi and Hirschauer,8 however, recognized the limitations of the GCS in the young child and developed the Child Coma Scale (CCS) to be used in children 1 to 36 months of age. Other investigators found that some children with seemingly mild head trauma and a GCS score of 12 or greater have evidence of brain injury on CT scan. 4,9,10

The present study was undertaken to determine the association between an abnormal cranial CT scan and factors including information such as a history of loss of consciousness, headache, and vomiting and clinical signs such as altered mental status, seizure, posturing, and focal neurologic deficits. We also evaluated the clinical findings in patients with a GCS score of 12 or greater and an abnormal CT scan.

METHODS

We retrospectively reviewed the medical records of all children aged 1 through 18 years who underwent a cranial CT scan for acute head trauma between January 1982 and December 1986. According to emergency department protocol, children with acute head trauma receive a cranial CT scan if they have any of the following clinical features: (1) history of loss of consciousness, progressive headache, and/or persistent vomiting, or (2) altered mental status, seizure, or focal neurologic deficit at the injury scene or in the emergency depart-

ment. The cranial CT scans were interpreted by a pediatric radiologist and were considered abnormal when any of the following were identified: (1) areas of increased or decreased density, (2) midline shift, (3) loss of gray matter-white matter differentiation, or (4) signs of herniation. Pathologic findings on CT scan included the following: (1) acute and subacute subdural and epidural hemorrhage, seen as a hyperdense collection alongside the cerebral hemisphere with or without midline shift; (2) cerebral edema with loss of gray matter-white matter differentiation with or without midline shift; (3) parenchymal hemorrhage that appears as areas of increased density and irregular margins within the cerebral hemisphere; and (4) herniation, usually evident by obliteration of the basal subarachnoid cisterns. The following patient information was collected: age, sex, historical information (loss of consciousness, vomiting, headache, seizure), physical findings, results of head CT scan, treatment, and outcome. The GCS score was calculated for all patients with normal mental status on admission to the emergency department.

The severity of head trauma was determined according to the following four variables: (1) altered mental status, defined as a history or physical findings of unresponsiveness or an inappropriate motor response to verbal or painful stimuli; (2) evidence of increased intracranial pressure, defined as the presence of persistent and/or progressive headache or persistent vomiting; (3) seizure or focal neurologic deficit; and (4) scalp and/or facial injuries, defined as hematoma, contusion, and/or laceration. Severity was considered mild if none of the above was present; moderate if only facial or scalp hematoma, contusion, or laceration was present; and severe if one or more of the first three variables were

Clinical findings of children with normal and abnormal CT scans were compared by the Fisher's exact and χ^2 tests. The t test was used to evaluate the age difference between these two groups. All tests were two-tailed.

RESULTS

Ninety-one patients underwent cranial CT scan for acute head trauma during the study period. Thirty-six patients were excluded because they were either less than 1 year old or had underlying coagulopathy. Of the 55 remaining patients, 36 were boys and 19 were girls. The age range was 12 months to 15 years, with a median age of 6.7 years. Severity of head trauma was determined according to the presence or absence of clinical variables.

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| Table 1.—Clinical Findings in Patients With Severe Head Trauma | | | | | | | | | | |
|--|-------------------|--|--|--|--|--|--|--|--|--|
| | | No. of Patients by Computed Tomographic Scan Finding* | | | | | | | | |
| Clinical Finding | Positive (n = 37) | Negative (n = 7) | | | | | | | | |
| Altered mental status | 31 | 0 | | | | | | | | |
| History of loss of consciousness, min | 6 | 2 | | | | | | | | |
| >5 >5 | 12 | 2 | | | | | | | | |
| Vomiting | 15 | 5 | | | | | | | | |
| Headache | 11 | 2 | | | | | | | | |
| Focal neurologic deficit | 7 | 0 | | | | | | | | |
| Seizure | 7 | 0 | | | | | | | | |
| Soft-tissue injury | 16 | 1 | | | | | | | | |

^{*}All patients had more than one variable present.

| P | atient No./ Age, y | Loss of Consciousness, min | Headache | Vomiting | Seizure | Focal Neurologic Deficit | Computed Tomographic Scan Finding | | | | |
|---|-----------------------|----------------------------------|----------|----------|--------------------------------|--------------------------------|--|--|--|--|--|
| | 1/14 | <5 | Yes | Yes | No | No | Parenchymal hemorrhage | | | | |
| | 2/9 | None | Yes | No | No | No | Epidural hematoma | | | | |
| | 3/13 | None | Yes | Yes | No | No | Epidural hematoma | | | | |
| | 4/3 | <5 | No | Yes | No | No | Subdural hematoma | | | | |
| | 5/2 | >5 | No | No | <1 min (at the accident scene) | No | Subdural hematoma | | | | |
| | 6/13 | None | Yes | Yes | No | No | Epidural hematoma | | | | |

| Table 3.—Abnormal Computed Tomograp Findings* | |
|---|-------------------------|
| Type of Lesion | No. (%)† of Patients |
| Subdural hematoma | 7 (18.4) |
| Epidural hematoma | 15 (40.5) |
| Parenchymal hemorrhage | 8 (21.6) |
| Subarachnoid hemorrhage | 6 (16.2) |
| Cerebral edema | 2 (5.4) |

*One patient had subdural and epidural bleeding. †The percentage given is for the specific type of lesion found on computed tomography in relation to the total number of abnormal computed tomographic scans.

Forty-four patients had severe head trauma, of whom 37 (84%) had abnormal CT scans. The clinical findings of all 44 patients are summarized in Table 1. Six patients with severe head trauma and abnormal CT scans were described as being alert, oriented, and without any neurologic deficit at the time of examination in the emergency

department; all had a GCS score of 12 or greater. The clinical findings in these patients are summarized in Table 2. Three patients in this group had an epidural bleed, and two required neurosurgical management.

Three patients were classified as having moderate and eight as having mild head trauma. None of the 11 patients in the mild and moderate groups had any evidence of brain injury or intracranial bleeding on their head CT scans. One patient in the moderate group had a depressed skull fracture that did not require treatment, and two patients in the mild group had a linear skull fracture.

Table 3 summarizes the CT findings in all patients with abnormal CT scans. Altered mental status was found in 31 patients (83.8%) with an abnormal CT scan. All patients with seizure or posturing on arrival at the emergency department had an abnormal CT scan. While the positive pre-

dictive value of seizure and focal neurologic deficit was 100%, their sensitivities were low (18.9%). The predictive value, sensitivity, and specificity of all clinical variables are listed in Table 4. When the group with abnormal CT scans was compared with the group that had normal CT scans, only altered mental status, focal neurologic deficit, and seizure or posturing were noted to be consistently associated with abnormal findings on CT scan. Altered mental status (P < .005) and severe head trauma (P < .002) were significantly associated with an abnormal CT scan. The associations between clinical variables and cranial CT scan results are summarized in Table 5.

COMMENT

Cranial CT scan serves a major role in the management of head trauma, as it accurately identifies the type and extent of brain injury secondary to trauma. High-yield criteria for urgent cranial CT scan in both medical and surgical adult patients are well established.11 Such criteria are not adequately addressed in the pediatric literature. Zimmerman et al4 reviewed the CT scan results in 286 patients with acute head trauma, half of whom were children. All patients were evaluated clinically at the time of presentation and assigned a clinical grade according to their mental status and the presence or absence of focal neurologic deficit. Neither the GCS score nor the detailed clinical findings of these patients were reported. However, 40% of the patients with minimal or no disturbance of consciousness had abnormal CT scan results. Rivara et al⁹ reviewed the clinical findings of 98 children with acute head trauma. Altered mental status and focal neurologic deficit were significantly associated with abnormal CT scans; however, 31% of the patients with a GCS score of 12 or greater had an abnormal CT scan. The GCS scale provides an easily used reproducible scoring system for evaluating patients with acute head injury.7 Finding intracranial injury in 25% of patients with a GCS score of 12 or greater in our study and in 31% by Rivara et al9 implies that the GCS may have limited application in the pediatric population. Similar observations have been made by other investigators. 4.9

Table 4.—Predictive Value, Sensitivity, and Specificity of Clinical Variables

| Clinical Variable | Positive Predictive* Value, % | Negative Predictive† Value, % | Sensitivity, %‡ | Specificity, %§ |
|---------------------------------|-------------------------------------|-------------------------------------|-----------------|-----------------|
| Altered mental status | 88.6 | 44.4 | 75.6 | 66.6 |
| Increased intracranial pressure | 58.6 | 66.6 | 73.9 | 50 |
| Seizure/posturing | 100 | 37.5 | 18.9 | 100 |
| Focal neurologic deficit | 100 | 37.5 | 18.9 | 100 |
| Severe head trauma | 74 | 100 | 100 | 27.7 |

*Percentage of patients with a variable who had an abnormal computed tomographic scan. †Percentage of patients without a variable who had a normal computed tomographic scan. ‡Percentage of patients with abnormal computed tomographic scans who had the variable. §Percentage of patients with normal computed tomographic scans who did not have the variable.

| | | o. (%) of P CT Scan I | | | P | |
|---------------------------------|------|--------------------------|----|----------------|-------|-----------------|
| Clinical Variable | | ormal = 37) | | ormal = 18) | Value | Test |
| Altered mental status | o+ / | 75 6\ | 4 | (00.0) | | |
| Present‡ | , | 75.6) 24.4) | | (33.3) (66.7) | <.005 | χ² |
| Increased intracranial pressure | ` | , | | | | |
| Present | 17 (| 74.0) | 12 | (50.0) | .092 | χ² |
| Absent | 6 (| 26.0) | 12 | (50.0) | .032 | X |
| Focal neurologic deficit | | | | | | |
| Present | 7 (| 18.9) | 0 | 1 | .082 | Fisher's exact |
| Absent | 30 (| 81.1) | 18 | (100) ∫ | .502 | ribilot 3 GAGOE |
| Seizure Present | 7 (| 18.9) | 0 | ì | | |
| Absent | , | (81.1) | 18 | (100) | .082 | Fisher's exact |
| Severe head injury | | | | | | |
| Present | 37 (| (100) | 13 | (72.2) | <.002 | Fisher's exact |
| Absent | 0 | | 5 | (27.8)∫ | | |

*CT indicates computed tomographic.

†Percentage given is for the specific finding among all patients (2 × 2 table [cumulative]). ‡Verbal, painful, unconscious.

These observations cause concern to the physician caring for the injured child, and the routine use of the GCS in classifying severity of head injury of children needs to be reevaluated. In 1984, Raimondi and Hirschauers recognized the limitation of the GCS when applied to children aged 1 to 36 months. This was attributed to immaturity of the central nervous system in the first 36 months of life, which makes interpretation of GCS scores difficult. Accordingly, they designed the CCS to be used in this age group. Our classification takes into consideration the major components of clinical evaluation, ie, historical data and findings on physical examination. Applying these criteria permitted identification of patients with intracranial injuries that would have been missed

had a GCS score of 12 or greater been the determinant for not performing a CT scan. Nevertheless, the present study is limited by its retrospective nature and the lack of precise ascertainment values for individuals in each group. Although a protocol for the management of head trauma and indications for obtaining a head CT scan were available during the study period, head CT scans were obtained for patients with mild or moderate head trauma either by less experienced physicians, ie, residents, or at the request of the private physician. Therefore, the predictive values, sensitivities, and specificities given in Table 4 must not be overemphasized. A prospective analysis of patients with all types of head injuries from mild to severe will yield the true values and confirm or reject the utility of any criteria or classification system.

We conclude that children who meet the historical and clinical criteria outlined for severe head trauma should be considered for immediate diagnostic cranial CT scan. Historical information and clinical examination are the most accurate predictors for abnormal CT scans in children with head trauma regardless of their GCS scores. In patients with moderate or mild head injury, obtaining a cranial CT scan may not alter management decisions. This group of patients may be discharged from the emergency department after complete neurologic examination, after being given monitoring instructions and being advised to return if they become symptomatic. Head CT scan should not be delayed in the child with symptomatic head trauma. A prospective study involving larger numbers of patients is needed to further evaluate the accuracy of such a classification.

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Adolescents With Closed Head Injuries

A Report of Initial Cognitive Deficits

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 Accidents represent the leading cause of morbidity in the adolescent age group. Closed head injuries (CHI) sustained in such accidents are frequently associated with cognitive deficits. The intent of this study was to explore the neuropsychological functioning of adolescents with CHI. Thirty-three teenagers who had sustained CHI as the result of a motor vehicle or motor vehicle/pedestrian accident were compared with orthopedically injured (n = 13) and matched, noninjured (n=35) control groups. Results indicated that immediately after injury, patients with CHI performed poorer than their counterparts on measures of intelligence, cognitive flexibility, memory (particularly verbal recall), and verbal fluency. Thus, the findings indicate that adolescents who sustain CHI experience pervasive cognitive deficits immediately after injury that potentially interfere with reentry into their home, school, and peer activities.

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Accidents have been well documented as the leading cause of mortality and morbidity in children and adolescents. In 1984, there were approximately 12.4 per 100 000 deaths in the 5- to 14-year-old age group and 49.4 per 100 000 deaths from accidents for individuals between 14 and 24 years (National Center for Health Statistics. personal communication, 1987). Further, 125 to 185 per 100 000 head injuries occur each year in these age groups. 1,2 Closed head injuries (CHI) often result in numerous temporary and/or permanent cognitive deficits. This study examined the neuropsychological functioning of adolescents immediately after CHI.

Head injuries resulting from accel-

eration/deceleration accidents (eg, motor vehicle accidents) often cause widespread shearing of nerve fibers. The frontal and temporal lobes are particularly vulnerable, and the functions of these areas are frequently disrupted.³ However, electroencephalographic (EEG) and computed tomographic (CT) scan results are often within normal limits, even when there is significant neuropsychological impairment.⁴

Investigators have reported that age is a prognostic factor associated with recovery from CHI. Adolescents have been believed to be more resilient than very young children (under 5 years old) or older adults. Because of this differential in recovery and the high rate of injury during adolescence, addressing cognitive impairment in this population is important. However, relatively little research has focused exclusively on teenagers.

Lowered intellectual functioning of children and adolescents with CHI has been reported. 6,7 When pre-CHI testing data were available, decrements of at least ten points were noted.8 Richardson,9 however, speculated that IQ declined as much as 30 points based on estimates of premorbid intelligence. Even when intellectual functioning is average, verbal and visual memory deficits may exist. Poorer information storage and long-term storage and retrieval have been found in head-injured patients.7.10 Slowed reaction time, difficulty with verbal expression, and visuospatial deficits have also been associated with CHI.11

Unfortunately, much of the research exploring the cognition of adolescents with CHI is methodologically flawed. Although age has been described as a prognostic factor, samples often include children, adolescents, and adults in one study. Analyses in these studies do not control for the subject's age. Additionally, many reports are based

on clinical impressions, case studies, or small sample sizes. Adequate control groups are infrequently employed, thus raising validity concerns.

Currently, there is an 18-month longitudinal research project under way to chart the recovery course of adolescents with CHI. As a part of this larger project, this study addresses the cognitive deficits that occur immediately after sustaining such an injury. Adolescents who sustained mild to severe CHI as the result of a motor vehicle accident were compared with a matched noninjured (NI) and an orthopedically injured control (OC) group. While the latter two groups were not expected to differ on various indexes of neuropsychological functioning, the CHI group was hypothesized to manifest impairments in intellectual functioning. cognitive flexibility, abstract thinking, memory, and verbal fluency.

SUBJECTS AND METHODS

A total of 81 subjects between 12 and 20 years old (mean age, 16 years) participated in this study; 39 (48.15%) were female and 42 (51.85%) were male. All subjects were enrolled in school at the time of recruitment and had a mean education level of 10.16 years.

Subjects were classified into three groups. The first group comprised 33 adolescents who were admitted to a large university hospital subsequent to a motor vehicle or motor vehicle/pedestrian accident and had sustained a CHI. The CHI was documented in the medical record and included a loss of consciousness. The second group was an NI control group of 35 teenagers. These adolescents did not have a history of head injury and were recruited from nearby schools and through bulletin board announcements in the community. Based on an initial screening interview that was conducted by telephone, subjects were matched with the CHI group for age, sex, race, and approximate socioeconomic status based on report of parental employment and level of education. Third, an OC group consisted of 13 teenagers who were

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admitted to the hospital following accidents similar to the CHI group. These subjects sustained orthopedic injuries that required hospitalization. However, there was no loss of consciousness or documentation of head injury in their medical records. Several patients had multiple orthopedic injuries and surgery was required. According to parental report, adolescents in this group did not have a history of CHI. This group was used to control for the effects of hospitalization but was not matched with the CHI group.

Injured subjects were admitted to either a Shock Trauma or Intensive Care Unit at a large hospital where they received their immediate care. The parents of patients who met criteria of this study (eg, adolescent, enrolled in school, and injured in motor vehicle-related accident) were contacted, informed of the project, and asked to participate. For all three groups, informed consent was obtained from both the subjects and their parents.

Parents of all subjects completed a medical history questionnaire devised for this study that assessed difficulties during mother's pregnancy, neonatal problems, developmental delay, and history of neurologic dysfunction. Injured subjects received a physical examination by a pediatrician during their hospitalization, and physicians provided a composite score of extent of injury according to Glasgow Coma Scale (GCS)12 and the Modified Injury Severity Scale.18 When CT scan, EEG, and neurometric testing (quantitative assessment of brain activity and processes) had been conducted as part of the patient's hospitalization course, results were obtained. In addition, the length of the hospital stay was recorded.

Neuropsychological functioning was assessed by a series of standardized tests. Depending on the age of the subject, the Wechsler Intelligence Scale for Children-revised¹⁴ or Wechsler Adult Intelligence Scale-revised¹⁵ was used to measure intellectual functioning. Cognitive flexibility was assessed by the Wisconsin Card Sort Test¹⁶ and the Halstead-Reitan Trail Making Test.¹⁷ The Wechsler Memory Scale¹⁸ and Selective Reminding Test¹⁹ were used to assess for recall of visuospatial and verbal information. Verbal fluency was assessed by the Controlled Oral Word Association Test (Table 1).¹⁹

Assessments were conducted as soon as patients were alert, oriented, and medically stable. Noninjured subjects were evaluated at the time of entry into the study. All assessments were conducted by a psychometrician or graduate student in clinical psychology who had been trained to administer the neuropsychological tests. The battery took approximately three hours to complete.

Table 1.—Measures Used to Assess Cognitive Abilities

Ability Assessed Wechsler Intelligence Scale for Children-revised Intelligence Wechsler Adult Intelligence Scale-Intelligence revised Wisconsin Card Sort Test Cognitive flexibility Trail Making Test Cognitive flexibility Wechsler Memory Scale Verbal and visuospatial memory Verbal memory and new learning ability Selective Reminding Test Controlled Oral Word Association Verbal fluency

Table 2.—Intellectual Functioning Immediately Following Closed Head Injury (CHI)

| | | Group Means | | |
|---------------------|-------|-----------------------|-----------------------|-------------------|
| Variable | СНІ | Orthopedic Control | Noninjured Control | <i>F</i> Ratio |
| Full-Scale IQ | 90.75 | 103.75 | 109.83 | 11.94* |
| Verbal IQ | 93.09 | 105.17 | 107.77 | 7.41* |
| Performance IQ | 90.06 | 102.08 | 109.83 | 13.44* |
| Information | 7.42 | 9.00 | 10.17 | 7.03† |
| Digit Span | 9.03 | 10.17 | 9.69 | 0.68 NS‡ |
| Vocabulary | 8.58 | 8.77 | 10.14 | 3.42§ |
| Arithmetic | 8.73 | 9.83 | 10.83 | 3.58§ |
| Comprehension | 8.33 | 9.17 | 10.51 | 4.49† |
| Similarities | 9.27 | 9.83 | 11.69 | 5.65† |
| Picture Completion | 9.45 | 9.83 | 11.03 | 2.31 NS‡ |
| Picture Arrangement | 8.56 | 10.58 | 10.43 | 4.74† |
| Block Design | 9.06 | 9.92 | 11.89 | 7.55* |
| Object Assembly | 7.94 | 8.58 | 11.31 | 11.74* |
| Digit Symbol | 6.91 | 9.77 | 10.91 | 12.62* |

^{*}P<.001.

§P<.05.

RESULTS

For the purposes of analysis, subjects were divided by injury status (CHI, OC, or NI). There were no significant differences between groups regarding race or socioeconomic status. However, the OC group was older (mean age, 16.98 years) than the CHI group (mean age, 15.58 years).

Medical Data

The GCS score ranged from 4 to 15 with a mean of 11.59. Ten patients had a severe CHI (GCS = 3 to 8), three had moderate injury (GCS = 9 to 12), and 21 had mild CHI (GCS = 13 to 15). Based on physical examination, 24 (72.73%) of the subjects in this group hit the left side of their head while 11 (33.33%) hit the right side. Intracranial abnormalities on CT scan were noted in the left and right hemisphere of the brain for 16 (48.48%) and five

(15.15%) of the patients with CHI, respectively. In addition, abnormal results of the CT scan (skull) were found for nine (27.3%) of the patients with CHI; eight (24.2%) had abnormal EEG findings; and nine (27.3%) had abnormal results of neurometric examination. No differences were found between the CHI and OC groups on their Modified Injury Severity Scale scores or the length of their hospitalization. According to parental report, there were no differences between groups with regard to difficulties with mother's pregnancy or delivery, the attainment of developmental milestones, known neurologic deficits, or a history of psychiatric problems.

Neuropsychological Data

Analyses of variance were conducted to determine which cognitive variables differentiated the groups. The α level for individual comparisons was set at P < .01. Post hoc pair-wise

[‡]NS indicates not significant.

| | | • | | |
|------------------------------|-------|-----------------------|-----------------------|-------------------|
| Variable | СНІ | Orthopedic Control | Noninjured Control | <i>F</i> Ratio |
| Wisconsin Card Sort Test | | | | |
| Categories, No. | 5.57 | 5.77 | 5.89 | 1.01 NS* |
| Cards, No. | 90.66 | 88.00 | 79.31 | 3.05† |
| Perseverative errors, No. | 13.73 | 12.92 | 8.60 | 3.08† |
| Nonperseverative errors, No. | 9.00 | 7.92 | 4.71 | 3.50† |
| Trail Making Test | | | | |
| A | 36.94 | 22.00 | 27.17 | 7.29‡ |
| В | 88.72 | 50.31 | 58.74 | 7.62‡ |

^{*}NS indicates not significant.

[‡]P<.01.

| | 4 | 3 | | |
|---|-------|-----------------------|-----------------------|-------------------|
| Variable | СНІ | Orthopedic Control | Noninjured Control | <i>F</i> Ratio |
| Wechsler Memory Scale Verbal (Immediate) | 6.00 | 8.35 | 7.96 | 5.16* |
| Verbal (Delayed) | 4.45 | 6.89 | 6.29 | 5.43* |
| Visuospatial (Immediate) | 9.84 | 11.50 | 11.62 | 2.91 NS† |
| Visuospatial (Delayed) | 8.42 | 10.17 | 11.26 | 5.99* |
| Selective Reminding Test Trials, No. | 10.62 | 8,46 | 9.66 | 2.54 NS† |
| Cued Recall | 9.39 | 10.69 | 10.06 | 3.22‡ |
| Recognition | 11.44 | 11.92 | 12.00 | 4.13* |

^{*}P<.01.

[‡]P<.05.

| | Group Means | | | | | | |
|-----------------------------|-------------|-----------------------|-----------------------|-------------------|--|--|--|
| Variable | СНІ | Orthopedic Control | Noninjured Control | <i>F</i> Ratio | | | |
| FAS* (average No. of words) | 10.42 | 14.33 | 13.46 | 6.09† | | | |
| Animal (No. of words) | 15.33 | 20.92 | 19.31 | 7.99‡ | | | |

^{*}FAS indicates words that began with the letters f, a, and s.

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comparisons were employed using the Scheffé procedure.

As expected, subjects with CHI performed more poorly on several indexes of cognitive functioning than the NI controls. They had lower Verbal, Performance, and Full-Scale IQ scores (P<.001) than both the NI and OC groups. With the exception of Digit Span and Picture Completion, NI subjects performed better on all intellectual subtests than patients with CHI (P<.05 to P<.001). In addition, subjects with CHI were more impaired than their OC counterparts on Picture

Arrangement and Coding/Digit Symbol and subjects in the OC group were more impaired than their NI counterparts on Block Design or Object Assembly (Table 2).

Adolescents with CHI had more difficulty than subjects in the OC and NI groups on tasks that required sequencing ability and cognitive flexibility such as the Trail Making Test (P<.001). A similar pattern of performance was noted on the Wisconsin Card Sort Test. Groups were able to complete a comparable number of categories, but the CHI group made more

perseverative (P<.05) and nonperseverative (P<.05) errors and used more cards to complete the task (P<.05) (Table 3).

As measured by the Wechsler Memory Scale, memory deficits emerged, with teenagers in the CHI group having more difficulty in their delayed recall of visuospatial information as compared with the NI group (P < .05). Immediate and delayed recall of verbal-contextual material (P < .01) was poorer for patients with CHI than for subjects in the OC or NI groups. Memory impairment was also evident on the Selective Reminding Test. Even when the stimulus words were presented in a multiple-choice format, adolescents with CHI recognized fewer words than their NI counterparts (P < .05). In addition, they were less able than the OC group to utilize phonemes to facilitate recall (P < .05)(Table 4).

Verbal fluency was assessed by the Controlled Oral Word Association Test. When asked to generate words that began with the letters f, a, and s, the CHI group produced fewer words (P<.01). They also listed fewer words within a particular category (P<.001) (Table 5).

COMMENT

Results of this study support the hypothesis that adolescents with CHI manifest more difficulties with intellectual functioning, cognitive flexibility, verbal fluency, and memory abilities immediately after injury than teenagers in an OC group or NI control group. This is consistent with literature that asserts head injury disrupts numerous thought processes.20 When compared with the control groups, general intellectual impairment of teenagers with CHI was evident on Full-Scale, Verbal, and Performance IQ. Teenagers with CHI performed more poorly than the NI controls on all but two of the subtests (Digit Span and Picture Completion).

The Vocabulary subtest is believed to be less affected by injury and is more indicative of a premorbid level of functioning.²¹ In this study, the adolescents with CHI scored lower on this measure than their peer counterparts. This suggests that CHI is associated with global intellectual decline. The possibility also exists that the adoles-

[†]P<.05.

[†]NS indicates not significant.

[†]P<.01. ‡P<.001.

cents with CHI had lower preinjury intellectual capacities and that limited abilities actually put these teenagers at risk to get into accidents. This support speculation investigators22 that individuals who are involved in accidents represent a select group with a history of behavioral and family problems.

Surprisingly, with the exception of Picture Arrangement and Coding/ Digit Symbol, teenagers in the OC and CHI groups were similar on their subtest scores. There are three possible explanations for this that cannot be ruled out on the basis of this study. First, although adolescents with orthopedic injuries were well oriented at the time of their evaluation, many were quite uncomfortable because of their injuries. This may have interfered with their ability to perform optimally. Second, there is the possibility of undetected mild head injuries in patients who were believed to have only sustained orthopedic injuries. Third, the question is raised, once again, as to whether or not adolescents who get into accidents have premorbid intellectual impairments.

The difficulties that emerged in the sequencing abilities and cognitive flexibility of subjects with CHI are consistent with frontal lobe injury. Teenagers with CHI had more difficulty shifting cognitive sets quickly, using feedback to deduce a conclusion and performing tasks of cognitive abstraction. In addition, the greater number of perseverative errors parallels findings by Cicerone et al,23 who found that damage to the frontal lobe in adults contributes to a perseverative tendency. Although the majority of adolescents with CHI did not have focal findings in the frontal lobes, these results suggest that diffuse injury is associated with problems in this area.

While no differences were noted in teenagers' immediate recall of visuospatial material, the CHI group was able to retain less information over a 30-minute span of time. Moreover, impairments were noted in both immediate and delayed recall of verbal-contextual material. When information was presented in a more simplified format, the groups were able to recall a list of words over a series of repeated trials. However, teenagers

with CHI had more difficulty using phonemic cues to facilitate recall and were less able to recognize the learned words. Thus, adolescents with CHI appear to use different strategies to recall information and have difficulty retrieving complex verbal information because their strategies are less effective and information is encoded in a less-organized fashion.

Overall, adolescents with CHI had more difficulty recalling verbal as opposed to visuospatial material. Although lateralization of injury was not incorporated into the design of this study, the vast majority of these subjects hit the left side of their head and approximately half had abnormal left hemisphere findings on their CT scan. By contrast, fewer subjects hit the right side of their head or had right hemisphere abnormalities. Thus, the results of this study are consistent with research that has found verbal memory impairment to be associated with injury to the left hemisphere of the brain. Poorer performance by the CHI group on measures of verbal fluency is also consistent with injury to the left hemisphere.

Past research has associated cognitive deficits with injury to specific areas of the brain. Subjects with CHI in this study were not classified according to focal injury. However, CHI is characterized by the widespread nature of the injury, and focal findings are often not found on CT or EEG. These findings highlight pervasive impairment consistent with diffuse in-

In conclusion, the results of the study indicate that adolescents experience numerous deficits immediately subsequent to CHI. These cognitive limitations have direct implications for their return to their families, schools, and communities and need to be considered in establishing realistic expectations for these teenagers. To more completely understand CHI in this population, future research will need to address the premorbid characteristics of youth who are involved in such accidents, the course of their recovery, and the differences in deficits depending on severity and site of injury.

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Risk Factors for Injury in a 3-Year-Old Birth Cohort

Charles P. Larson, MD, MSc, I. Barry Pless, MD, FRCPC

• The purpose of this study was to identify factors associated with injuries in the first three years of life and to assess their predictive utility. The parents of 918 children (82% of an eligible birth cohort) completed a telephone interview to document injury histories. The occurrence of injury was then linked to previously obtained information characterizing early childhood. Several determinant associations were found for injuries seen by a physician and for those requiring treatment. Maternal factors (single, unemployed, smoking) were dominant in both instances. From these factors, logistic regression models were developed from which adjusted relative risk estimates were derived. The presence of all three maternal factors, as well as the absence of a younger sibling, increases the probability of an injury from 20% to over 60%. These findings may be used to assist in the development of preventive programs by targeting children at increased risk. They also provide a basis for further studies that will permit a better understanding of the causal mechanisms linking maternal factors to preschool injury. (AJDC 1988;142:1052-1057)

It has long been recognized that injuries are the leading cause of childhood mortality after 1 year of age and a major cause of morbidity and disability throughout childhood. 1-7 Injury incidence rates have consistently been shown to be relatively high in 2- to 3-year-old children, with a second peak occurring in teenagers. 3.5.8 Annual incidence rates in preschool-age children vary from 10% to 20%. 2.3.5.9

The goal of this investigation was to identify factors associated with injuries occurring between birth and 3

years of age and to assess their predictive utility. Earlier investigations have identified several factors that characterize children who have injuries in terms of their health, 7,10,11 behavior, 9,10,12-14 family/social environand physical ment15-19 environment.2,5,7,20-22 Unfortunately, the reported findings have been inconsistent. This has led some investigators to conclude that it is presently impractical to try to identify, for preventive purposes, children at increased risk for injuries on the basis of such characteristics. 15,16

However, many of the earlier injury investigations have been based on historical (retrospective) data obtained from incident cases and injury-free controls. Such studies are subject to recall bias, and the breadth of the factors that may be investigated is limited. In contrast, in this investigation, injured and noninjured 3-year-old members of a birth cohort were compared for differences in a wide range of prospectively obtained health, psychosocial, and environmental information characterizing early childhood.

PATIENTS AND METHODS Design Overview

Parents of a 1-year birth cohort completed repeated interviews at two weeks and 6, 12, and 18 months postpartum, to chronologically document a broad set of health, psychosocial, and environmental factors. The cohort was resurveyed cross-sectionally during their fourth year of life.

The interviewers followed a written protocol and were assessed at the beginning of and during the study period for uniformity of style. No interobserver reliability estimates were made, nor were health records examined to confirm the validity of the responses. However, it has been shown that parent recall for such events is generally acceptable.²⁸

Study Population

Any child born in 1983 whose mother resided within a designated Montreal community health district was eligible for entry into the cohort. As shown in Table 1, this group is very likely to be typical of many urban, multiethnic communities. Exclusion criteria included teenage pregnancies (mothers of 17 years of age or less), mother or newborn hospitalized longer than ten days postpartum, and families intending to move outside the district prior to the birth of their child. Of the 2214 documented births, 2075 families were contacted. One hundred ninety-three families were excluded, and 377 refused to participate, leaving an initial enrollment of 1505 (72%). At 18 months postpartum, 1116 families remained in the study. Among these, 918 (82%) were interviewed by telephone during a four-week period in November 1986. families differed significantly (P < .05) from the cohort at entry in terms of family income (higher) and marital status (fewer single parents), but not by the mother's mean age or mother's years of education

Outcome Identification

As part of the follow-up interview, parents were asked if their child had ever had an accident treated by a physician. For each episode, parents were asked to describe the type, place, supervision, treatment, and consequences of the injury. For treatment, parents were given three response options: child hospitalized, received medical or surgical treatment, or seen by a physician but no treatment provided. Those for whom the first or second option was reported were classified as "treated" injuries.

Determinant Factors

Factors included in the analyses are summarized in Table 2. These were grouped under four broad headings: (1) maternal, (2) social/behavioral, (3) child, and (4) environmental. Certain factors are age specific, as indicated in Table 2. A 50% random sample of families received home visits at six weeks and 6, 12, and 18 months postpartum. During these visits, measures of

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Table 1.—Demographic Characteristics at the Time of Entry of the Entire Cohort and Those Remaining in the Study in the Fourth Year of Follow-up

| Characteristic | % of Entire Cohort | % of Those Remaining at Fourth Year of Follow-up |
|-----------------------------------|--------------------|--|
| Mother's education, y ≤10 | 19.6 | 16.2 |
| 11-13 | 31.1 | 32.0 |
| 14-16 | 31.2 | 31.8 |
| ≥17 | 18.1 | 20.0 |
| Family income, \$ <15000 | 32.4 | 22.3 |
| 15 000-24 999 | 24.9 | 26.8 |
| 25 000-44 999 | 24.5 | 27.3 |
| ≥45 000 | 18.2 | 22.0 |
| Marital status Single | 22.9 | 17.2 |
| Separated/divorced | 1.6 | 1.1 |
| Married/with father | 75.6 | 81.7 |
| Mother's first language French | 26.5 | 28.2 |
| English | 29.4 | 31.4 |
| Other | 44.1 | 41.4 |
| Mother's mean age, y | 28.0 | 27.9 |

the home environment²⁴ and maternal behavior²⁵ were completed by trained observers unaware of the objectives of the study.

Analysis

 χ^2 , or t test, statistics were calculated for the bivariate associations between potential determinant factors and the occurrence of any injury or a treated injury by the fourth year of life. Factors significantly (P < .10) associated with either outcome were then considered further. This first step was used simply to "screen" variables, and this accounts for the use of the unconventional probability level. Although repeated tests were performed, thereby increasing the risk of alpha error, no adjustment, eg, Bonferroni, was performed because these results were not used to test hypotheses. Factors identified in the first step were assessed for multicollinearity, ie, variables highly correlated with one another. Logistic regression models were subsequently tested to determine the extent to which the predictors were associated with an increased risk for injury by the fourth year of life. The logistic regression analyses were also used to determine the effect of multiple determinant factors on the likelihood and adjusted relative risk estimates for injury.

RESULTS

A history of one or more medically attended injuries was obtained in

32.7% (n=300) of the children at the follow-up interview during the fourth year of life; 66.0% (n=198) of these children had an injury requiring treatment. Twelve children (4.0% of those with injuries) were hospitalized. Of those who had injuries (treated and untreated), 73% had one, 19% had two, and 8% had three or more injury episodes. Table 3 describes the type of injury, the place of occurrence, and the parent's judgment of the adequacy of supervision.

Table 4 summarizes the results of the bivariate analyses for factors significantly associated with a history of any injury or a treated injury. (Significance was set at $P \le .10 \ [\chi^2]$.) This table includes a categorical description of the identified predictors and crude relative risk estimates for the occurrence of injuries at both levels of severity. Significantly elevated risks for either outcome were found for children of single, unemployed, smoking mothers, and for those without a younger sibling. The predominant grouping associated with either level of injury were those included under "maternal factors."

The results of the logistic regression analyses relating variables to the risk of any injury or a treated injury by

Table 2.—Early Childhood Factors Included in the Analyses Child's Age at Time Information Was Obtained, Factor wk (mo) Maternal factors Marital status (6, 12, 18) **Employment status** 2 Age Education 2 Maternal behavior 6 (6, 12, 18) 2 (6, 12, 18) **Smoking** Breast-feeding 2 (6) Health 2 (6, 12, 18) Parity 2 locial/behavioral factors Postpartum help 2 Family risk assessment 2 Father's caretaking role 2 (6, 12, 18) Alternative childcare (6, 12, 18) No. of children 4 y Younger sibling 4 y Infant car seat 2 (6) Child factors 2 Gender Neonatal illness 2 Acute illnesses (6, 12, 18)

Chronic illness

Immunizations

Family income

household

invironmental factors

Occupation, head of

Home environment

(6, 12, 18)

(6, 12, 18)

6 (6, 12, 18)

2

the fourth year of life are summarized in Table 5. This table provides adjusted relative risk estimates for the occurrence of injury, by adjusting for the influence of the other factors entered into the model. The adjusted and crude relative risk estimates are fairly similar, suggesting that the effect of each factor on injury outcome is relatively independent of the other factors in the model. The effect of specific combinations, eg, single and smoker, may be derived by multiplying the odds ratios for each.

The Figure illustrates the cumulative probability estimates, expressed as a percentage, for the occurrence of an injury requiring treatment by the fourth year of life. These estimates are derived from the regression coefficients in the final likelihood equation

Table 3.—Characteristics of Injuries by Type, Location, and Quality of Supervision % (No.) of Injuries Not Characteristics Treated Treated Total Type of injury 62.8 (76) 57.0 (142) 58.9 (218) Burn 2.5 (3) 10.4 (26) 7.8 (29) Poisoning 4.1 (5) 6.4 (16) 5.7 (21) Motor vehicle/pedestrian accident 1.6 (4) 1.1 (4) 30.6 (37) 24.5 (61) 26.5 (98) 65.0 (78) 76.3 (190) 72.4 (268) Adjacent to home 16.7 (20) 7.6 (19) 10.5 (39) Day care 2.5 (3) 1.6 (4) 4.6 (17) Recreational site 4.2 (5) 4.8 (12) 3.8 (14) Street 5.8 (7) 2.8 (7) 1.9 (7) Other 5.8 (7) 6.8 (17) 6.5 (24) Lacking 38.5 (42) 42.2 (97) 41.0 (139) Questionable 14.7 (16) 13.9 (32) 14.2 (48) Adequate 46.8 (51) 43.9 (101) 44.8 (152)

COMMENT

The descriptive characteristics of the injuries sustained by this preschool-age birth cohort are similar to those reported by other investigators. This includes the large proportion of injuries occurring in the home and those resulting from falls. 3,4,26 Following a review of the history, the interviewer judged supervision to be questionable or lacking in over 50% of injuries. This finding reemphasizes the importance of adequate supervision in this relatively immature, impulsive age group.

The main goal of this investigation was to identify predictors of the occurrence of one or more injuries between birth and the fourth year of life. Two levels of injury severity were included in the analyses. The "any injury" outcome is similar to most other investigations that define an injury simply on the basis of a physician encounter. However, because information was obtained on treatment received it was also possible to restrict the analysis to those with more severe injuries ("treated injuries"). Important differences in the risk factors and logistic regression models support the decision to conduct these separate analyses.

From the wide range of health, psy-

chosocial, and environmental factors assessed, several significant associations were identified. Factors descriptive of the mother were most frequently associated with both any injury and treated injuries. Maternal determinants (risk factors) included being single, unemployed, and a smoker. While these characteristics often coexist in isolated, disadvantaged populations, it is noteworthy that increased risk among children of lower income or poorly educated mothers was not found in this study. This is consistent with other investigations of this association in preschool-age children. 7,8,12,16,18 The fact that smoking. single status, and unemployment have significant associations with injury, while low family income and low educational level do not, may reflect the subtle but important difference between these elements. Income and educational level are associated with general or chronic family disadvantage, whereas the risk factors cited (smoking, single, unemployed) are more specific markers of personal

The maternal behavior scale used in this study is based on direct observations of the mother's interaction with her child and of her parenting skills.²⁵ The more varied the quality of interaction and the more proficient the

parenting skills, the higher the score. Only the total score at six weeks' postpartum follow-up was significantly associated with injury and this was limited to "any injury." It was expected that if the parent were more skillful, the child would have fewer injuries. The relationship was, however, inversely proportional to injury rates. Although it could be postulated that parents with better parenting skills are simply more candid or more accurate than those with poor skills, this is unlikely since the association was only found with the less-serious injuries. A more tenable explanation is that an "accepting" attitude by the mother (indicating more proficient parenting skills) allows more freedom of activity on the part of the child, thereby giving rise to more minor accidents. Since this heightened risk does not extend to more serious injuries, more permissive caretaking is probably not indicative of less-close supervision. Thus, having minor, untreated injuries may indicate a protective effect against more severe injuries.

No child factors were associated with the occurrence of an injury. However, the factors considered in the analysis were limited to descriptors of the child's physical health and not to developmental or behavioral factors that may also have important links to childhood injury. 9,13,27,28 The lack of association with health measures has been noted by others. 12

Children with a chronic illness and children of single mothers were at significantly greater risk for the occurrence of a treated injury, with both elevated crude and adjusted relative risks found. In an investigation of accident repeaters, Husband and Hinton¹⁷ found coexistent psychiatric or organic illness in other family members in 50% of their sample as well as high rates of family discord and single mothers (29%). Other studies in which an assessment of the child's physical health was included as a possible determinant have shown conflicting results, although few are restricted to preschool-age children. For example, in an unpublished study (I.B.P., C.S. Peckam, MD, C. Power, MD, unpublished data, 1988), the presence of

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| | % of Si | bjects | | Crude | | | | |
|---|----------------------|--|--------|--|--|--|--|--|
| Factor | Injury | No Injury | P | Relative Risk (95% Confidence Interval | | | | |
| Maternal civil status | ny Injur | y | | , | | | | |
| With father* | | | .014 | | | | | |
| Single | 14.7 | 9.3 | .014 | 1.7 (1.1, 2.6) | | | | |
| Maternal work status (by 18-mo follow-up) Working* | .,, | ،] | .075 | , | | | | |
| Not working | 56.7 | 49.7 | .075 | 1.3 (0.97, 1.8) | | | | |
| Maternal smoking (cigarettes) Nonsmoker* | | | .010 | ··· | | | | |
| Smoker | 36.7 | 28.3 | .010 | 1.5 (1.1, 2.0) | | | | |
| Maternal behavior score (6-wk follow-up), % Upper 75* | 84.4 | 71.5 | | · · · · | | | | |
| 11-24 | 8.2 | 18.2 | .025 | .37 (0.18, 0.76) | | | | |
| Lower 10 | 7.4 | 10.4 | | .66 (0.28, 1.5) | | | | |
| Social/behavioral factors Younger sibling Y* | | |) . | | | | | |
| N. | 72.1 | 65.9 | .058 | 1.3 (1.0, 1.8) | | | | |
| Tro | eated inj | ury | J | (| | | | |
| Maternal civil status | CONTROL DOSPINATIONS | - Carlia - Carrier Alexandria - Carrier Alexandria - Carrier - Car | } | management of management of management of the state of th | | | | |
| With father* | | | .002 | | | | | |
| Single | 17.3 | 9.4 | J | 2.0 (1.3, 3.2) | | | | |
| Maternal work status Working* | | |) | (| | | | |
| Not working | 60.8 | 49.7 | .016 | 1.6 (1.1, 2.3) | | | | |
| Maternal smoking (cigarettes) | 00.0 | 40.7 | J | ((,) | | | | |
| Nonsmoker* | | | | | | | | |
| Smoker | 37.5 | 29.4 | .034 | 1.4 (1.0, 2.0) | | | | |
| Age, y | | |)) | (| | | | |
| >30* | 27.0 | 31.7 | | | | | | |
| 26-30 | 33.0 | 36.9 | .075 | | | | | |
| 21-25 | 33.5 | 24.8 | .0,0 | 1.6 (.84, 3.0) | | | | |
| <21 | 6.5 | 6.5 |] | 1.1 (.85, 1.5) | | | | |
| Social/behavioral factors Younger sibling | | | ` | | | | | |
| Y | | | .029 | • | | | | |
| N | 74.6 | 66.2 |] | 1.5 (1.0, 2.2) | | | | |
| Alternate child care | | |) | ſ | | | | |
| 944, N* 34 Suo | | | .053 | | | | | |
| Y | 67.0 | 59.3 | j | [1.4 (1.0, 2.0) | | | | |
| Child factors Gender | | | | | | | | |
| Cender F* | | |) | | | | | |
| M | 55.7 | 48.7 | 100 | 1.3 (.94, 1.9) | | | | |
| Health problem at age 12 mo | | |) | (| | | | |
| N* | | | .085 | | | | | |
| ` Y | 19.9 | 14.2 | .005 | 1.4 (1.0, 2.0) | | | | |

^{*}Reference category for relative risk calculations.

significant visual or sensory deficits appeared to have a protective effect. In contrast, Manheimer and Mellinger, ²⁸ Bijur et al, ⁹ and Langley et al¹² all have reported a direct association with psychosomatic complaints, such as headaches and stomachaches.

The hypothesis that the parents of these children could have been sensitized to health events and thus reported more severe injuries is interesting but unlikely. Were this the case, the incidence of all injuries, not only severe ones, would have increased.

Elevated relative risks were also associated with the absence of a vounger sibling. The presence of a vounger sibling would be expected to result in an overall increased, though not necessarily additive, level of supervision being provided by the parents. To more thoroughly assess this possibility, a bivariate analysis of determinant factors for injury and the judged level of supervision was carried out. Significant associations with inadequate supervision were limited to mother's age (P=.052) and the absence of a younger sibling (P = .049). This latter result further supports the notion that supervision is a factor related etiologically to the occurrence of injury. Given that the absolute number of children in the home was not associated with injury, it may be that being the youngest increases risk.

The intent of the logistic regression analysis was to assess the predictive utility of the determinant variables identified through bivariate analyses. This procedure allows for the development of predictive models by entering only those factors significantly contributing to the likelihood estimate of injury. Factors are entered one at a time, with the order determined by the magnitude of their contribution to the estimate.

Common to both logistic regression models was maternal smoking. By what pathway does this factor influence the occurrence of injury? One may speculate that smoking serves as a marker for mothers whose inclination or ability to adequately supervise or protect a relatively dependent young child is diminished. This could be due to increased levels of stress or may indicate mothers who are less able to make wise decisions affecting their own health and the health and safety of their children.

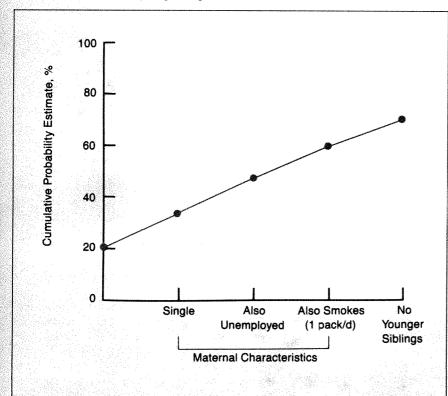
For the more severe, treated-injury outcome, several additional factors were entered into the logistic regression equation. These included two further maternal factors (marital and work status), the child's health at 12 months of age, and the presence or absence of a younger sibling. The addition of the maternal factors lends further support to the important role of the mother in explaining the occur-

Table 5.—Final Logistic Regression Models Relating Risk Factors to the Occurrence of Any Childhood Injury and Injuries Requiring Treatment

| Factor | Estimate | SE | P | Adjusted Relative Risk (95% Confidence Interval) |
|--|----------|------------|------|--|
| | Ā | ny Injury | | |
| Intercept | 70 | .14 | | • • |
| Maternal smoking, 1 pack (25 cigarettes)/d | .58 | .30 | .056 | 1.8 (1.3, 2.4) |
| Maternal behavior score (child age, 6 wk), % Upper 75* | |) | | ſ |
| 11-24 | 28 | .45 | .069 | .75 () |
| Lower 10 | 87 | .38 | | .41 (1.6, 3.5) |
| | | ated Injun | 1 | |
| Intercept | -1.4 | .17 | | * • * |
| Civil status With father* | |] | | · · · · · |
| Single | .68 | .27 | .013 | 2.0 (1.5, 2.6) |
| Work status Working* | |] | | (|
| Not working | .57 | .28 | .094 | 1.8 (1.3, 2.3) |
| Maternal smoking, 1 pack (25 cigarettes)/d | .36 | .20 | .074 | 1.4 (1.2, 1.8) |
| Health problem, child at 12 mo postpartum | | | | , , , |
| N* | |] | .016 | ··· |
| Υ . | .47 | .19 | .010 | 1.6 (1.3, 1.9) |
| Younger sibling | | 1 | | (|
| N. | .45 | .22 | .038 | 1.6 (1.3, 2.0) |

^{*}Reference category for relative risk calculations.

Cumulative probability for occurrence of injury by fourth year of life according to descriptors of mother and absence of young sibling.



rence of these injuries. The majority of injuries occur in the home and thus reflect the adequacy of parental supervision.

From the cumulative probability estimates simplified in the Figure, it can be seen that a child of a single, unemployed, smoking mother, who does not have a younger sibling, has a very high probability of sustaining an injury requiring treatment. Each of these factors makes an important independent contribution to the overall probability estimate. With the exception of smoking, however, none of the factors listed is amenable to community health interventions and none has a readily understandable link to injuries. This suggests that they may be serving as "markers" rather than being causative

These families received their medical care in Quebec and thus are covered by comprehensive national health insurance. Although it is reasonable to postulate that, in view of this, there may be a greater tendency to use health services for relatively minor problems indicating unimportant injuries, there is little evidence that this actually occurs to any significant extent.²⁹

Clinically, the factors identified in this study may serve as criteria for targeting children at elevated risk for injury. Parents of these children could be provided with augmented injury-prevention counseling. Inquiries aimed at identifying mothers in need of care-taking assistance or additional support should be made. This strategy is best suited to primary care settings.

This was an exploratory rather than directly etiologic investigation and did not stem from any a priori causal theory of preschool injury occurrence. Because of its exploratory nature, the data are properly viewed as forming a "developmental set," which must be confirmed using a different set of subjects. If confirmed, the risk factors identified may prove useful in the targeting of certain families. In particular, the results point to the important role that factors descriptive of the mother have in the prediction of preschool injury. Further study is needed to improve understanding of their causal linkage to preschool injury and

their potential applicability to prevention strategies.

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In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Epithelioid Germinal Centers in Overwhelming Childhood Infections: The Aftermath of Nonspecific Destruction of Follicular B Cells by Natural Killer Cells

Gregory S. Severson, MD; Douglas S. Harrington, MD; Sonny L. Johansson, MD, PhD; Bruce M. McManus, PhD (Arch Pathol Lab Med 1988;112:917-921)

Pediatric Perspectives



Abandonment, Infanticide, and Filicide

An Overview of Inhumanity to Children

Harry Bloch, MD

A child is nature's greatest creation. No ideal, harmony or mystery Can equal a child.

 ${f V}$ iolence to children has always existed and is one of the most intractable aspects of human behavior. Man has no aversion to child abandonment, infanticide, and filicide; nor has man hesitated to injure, cripple, strangle, smother, beat, overlay, burn, starve, drown, expose, enslave, poison, bury alive, bomb, and gas defenseless children, or to expose them to gene-altering Agent Orange, the deep, bodyburning and deforming white phosphorus and napalm, and the horrible effects of atomic bombs.2-8 This unending story through all the stages and structures of society from the primitive times to the 20th century, the motivations and forms of inhumanity to children, and some remedial measures are discussed herein.

Primitive man possessed little knowledge or skills and suffered severe handicaps in the struggle for subsistence. He lived as a nomadic hunter-gatherer, searching for food everywhere; and when children became an encumbrance to his essential migratory habits, they were abandoned to starvation and beasts.2,3,9 With the discoveries of agriculture and animal husbandry, man's roving ended and the process of civilization commenced. Concurrent with each stage and structure of its development, new reasons and methods of violence to children emerged.²⁻⁵

PRECHRISTIAN AND EARLY CHRISTIAN VIEWS

Ancient civilizations regarded children as omens of good and evil; and abandonment, infanticide, and filicide generated little concern. To seek favors or appease the gods, children were exploited in ritual sacrifice; to limit population growth and forestall uprisings, Egypt slew the male offspring of Jewish slaves; and in retaliation, God slew Egypt's male newborns. Entombed with dead parents in Egypt was a live child to give comfort and companionship; and until a few centuries ago, the Chinese and Japanese regarded female newborns as economic burdens and disposed of most of them by drowning. Ritual sacrifice was condoned by ancient Greece and Rome, and unwanted and deformed infants were exposed on dung heaps and devoured by wild beasts and birds, or salvaged for slavery and prostitution. 4,10,11 The Laws of Moses forbade ritual sacrifice, "Thou shalt not give any of thy seed to the idol Mollech"; and Jews cherished the hope that the Messiah numbered among their children.4,12 A particularly horrendous act of infanticide and filicide was perpetrated from the time of ancient Jericho (3000 BC) to modern Germany (1843)—the immurement of a child in the foundations of a new structure to assure stability, which, in its deed, was a manner of ritual sacrifice. 13

With the advent of Christianity, abandonment, infanticide, and filicide were banned; nonetheless, these crimes were neither lessened nor checked by church edicts (The Council of Neyra in 314), nor by the "shelters" established for abandoned and unwanted infants (in 737 in Milan, Italy, by Archbishop Datheus; in 1148 in Rome at the Hospital of the Holy Ghost; in 1444 in Florence, Italy, at the Spedali degli Innocenti; and in 1639 in Paris by St Vincent de Paul). Mortality reached such staggering numbers that these institutions were eventually forsaken.^{4,9}

In the Middle Ages, reasons and methods for child killing startlingly increased. It did not help any that the church hierarchy was all powerful, or that it castigated unmarried women, branded deformed newborns as omens of evil and products of consorting with demons and animals (which condemned the unfortunate mothers to stoning and drowning), or propagated the myth that "changelings" were replacements by Satan for the genuine infant. Furthermore, there were the common beliefs that infanticide was a venial sin, that parents had the power of life or death over their children, and that taking another's life did not include the newborn. 5 The oppression of serfs under the feudal system, the pressures for survival in deep poverty, and the cycles of famine and disease drove the impoverished serfs into violent crimes against children, especially female newborns who were judged expendable.2-5,11,14 Unwanted infants were dropped into sewers, ditches, fields, and forests or on roads, church steps, and dung heaps, or drowned. Fishermen often found infant bodies in their nets. 4.9.12 The worst disaster that befell children in the Middle Ages was the infamous "Children's Crusade" (1212). Fifty

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thousand children were prodded by priests to set off from France and Germany on a doomed quest to Jerusalem to recover the Holy Sepulcher. Few children escaped death, injury, disease, and abandonment.

16TH AND 17TH CENTURY ATTITUDES

The Elizabethan era (1558 to 1603), despite its intellectual and cultural prestige, proved incapable of bettering the lot of abandoned children. Many were reared in roguery, some as apprentices to masters often cruel and pitiless, and others were transported to the colonies to serve as indentured servants up to the age of 21 years. The good intentions of the Poor Law (1530), the Boke of Chyldren (1545) by Thomas Phaer (1510-1566) that pleaded for humanitarian care, and the act passed by Parliament to prevent the murder of "bastards" offered little relief. 4,5,15,16

The decay of feudalism in England was superseded in the 17th century by a progressive bourgeois society. Factories and mills employed young mothers who necessarily placed their infants in the care of wet nurses. These women were, with few exceptions, a deprayed lot who, after collecting a fee, disposed of their charges by overlaying, strangulation, smothering, or feeding the infants gin and wine. They then proceeded to wet nurse another unfortunate infant for a fee.²⁻⁵

INDUSTRIAL REVOLUTION

The swiftly accelerating Industrial Revolution in England (18th and 19th centuries) exerted a major influence on the incidence of sickly, deformed newborns and illegitimacy. These misfortunes have been accounted for by the rapacity of the factory lords, poverty of the workers, unhygienic conditions of the slums, and the moral consequences of the mass employment of girls and young women in factories and mills. The most grievous situation of the time was the lot and fate of child workers: a cheap, obedient labor force, who were victims of savagery and greed.8,17 In a sense, child workers were "immured" into a factory and mill, were often chained to the machines, worked six days a week, and on Sundays were forced to clean the machines. Children who ran away were lashed when caught and placed in ankle chains. Unemployed children filled the ranks of thieves and beggars. Charles Dickens (1812-1870) exposed the evils of child slavery (in David Copperfield and Oliver Twist) and depicted an England with an aristocracy of commerce dehumanized by acquired wealth, and of wretched, pitiful child workers. 18 Illegitimacy and abandonment of children by young domestics employed by the new wealthy and the aristocracy of blood who were made morally insensible by idleness and frivolity only began to wane after 1880, with the availability of contraceptives and abortion.19

The industrial growth in the United States was hampered by slavery, which had its singular tragedies for slave mothers whose young were brutally torn from their restraining arms and sold to distant plantations, never to be seen again. The alternative of filicide was sometimes chosen. The children of slaves were deprived of education, family ties, marriage, and, worse, were looked on as animals. 20,21 The Industrial Revolution resumed its progress at the end of the Civil War, and with it the evil of child labor became extensive—an evil not yet resolved. 22

'HOMES'

In the 19th century, the haven for unwanted and abandoned infants was the "foundling home." Catherine the Great of Russia, alarmed by the inordinate increase in abandonment and infanticide among unmarried women, founded "homes" that like "shelters" ended disastrously.²³ Similar experiences in the United States were slowly overcome at institutions conducted by the Sisters of Mercy.²⁴ Abraham Jacobi (1830-1919), a pediatrician, warned that infants collected in institutions die in large numbers (1872).²⁵

In England, a retired sea captain, Thomas Coram (1668-1757), saddened by the plight of abandoned children on the streets of London, founded a "home" in 1741. William Cadogan (1711-1797), seeking to reduce the frightful mortality and ailments suffered by children in these homes, presented his treatise, *Upon Nursing*

and Management of Children, in 1750. James Hanway (1712-1786), a London merchant, vigorously campaigned for better care. Robert Malthus (1766-1834), the English philosopher, claimed that the foundling home system was a sure way of increasing mortality, as did Jacobi in the United States. Charles Dickens in Oliver Twist wrote that no kind word at the "home" had ever lightened the gloom of Oliver's infant years. 14-16,18,18 Most deplorable was the indifference of wealthy English to the plight of poor children, evident by the closure for lack of support of the first dispensary for poor children founded by George Armstrong (1719-1789) in London, 15,16

The French Revolution (1789) made important contributions to child care. Better-conducted homes were opened, including Le Tour, to receive unwanted infants, and the Hôpital des Enfants Malades opened in Paris (1802) for the exclusive care of children.²⁶

20TH CENTURY AND WAR

In the 20th century, nations were not only in the vanguard of child brutality but were their principal enemy. Nazi Germany singled out Gypsy and Jewish children for brutal torture and extermination by the most infernal methods devised by humans. 27-38 Children were killed in gas chambers. burned to ashes in crematoria, tossed into the air and used for target practice, and snatched and pulled from the resisting arms of mothers and murdered. Children were injected with poisons, thrown into pits and buried alive, made victims of monstrous experiments, starved, made to stand through the night barely clothed in the frost, smashed against stone walls, had their skulls and bones cracked by tree trunks, and were flogged with rubber whips. In this manner, 1.5 million innocents were murdered.

Filicide by deliberate starvation is one of the most heinous crimes of the century. Millions of children suffer periodic episodes of devastating drought and famine, yet prosperous nations are lacking in the promptness of response and quantity of support needed to save the lives of children; in grants to support scientific methods of agriculture to prevent these catas-

trophies, and in the vital relief from the burden of foreign debts that leave few allocations for food, clean water, housing, medical and dental care, education and clothes—the basics to assure a happy childhood and future. There is enough food for all the children of the world; nevertheless, a "silent hunger" is the constant companion of children in the Third World, as is true for too many in the world of plenty.34

The darkest chapter of man's inhumanity to children has been war. 85 An atomic bomb strewed the streets of Hiroshima and Nagasaki with horribly burned and mutilated bodies of children.36 The war in Vietnam left children homeless and parentless, dead and wounded, maimed and crippled by shrapnel that tore through their bodies, genetically afflicted with Agent Orange, and scarred by deep, painful, deforming burns from white phosphorus and napalm.

THE FUTURE

In conclusion, violence to children has not been accidental. The motivations and methods have expanded from abandonment in primitive times to the diverse methods of injury and murder of children catalyzed with successive stages of civilization's development. The motivations have been economic (eg, greed, profit, poverty, insecurity, population control, class structure, and exploitation of labor); politics (eg, superpower dominance over Third World nations); ideologies (eg, fascism and philosophies of racial and ethnic superiority); war; education; insanity; and religion (eg, superstition, ritual slaughter, crusades, immurement, and antagonism to contraceptives, abortion, and illegitimacy).

We are swiftly reaching the 21st century. Will all the world's children be assured of freedom from hunger, war, and nuclear terrorism, and of access to clothing, clean water, shelter, affection, security, education, vocational training, and sports centers? Will they be free from the corruption of drugs, alcohol, and the violence of movies, television, and news media? Will they be given the opportunities of growing up physically, mentally, and emotionally strong, with a happy childhood and a secure future? Will each nation be the pediatrician for all of its children? Will violence to children be forever abolished? Will the suffering and the plight of deprived children, the hungry and homeless vanish? Is there a nation that cares about the rights of children?37,38

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Careers in Academic Medicine

Joseph S. Alpert, MD, Robert Coles, MD (Arch Intern Med 1988;148:1906-1907)

Efficacy of Leuprolide Therapy in Children With Central Precocious Puberty

Michael S. Kappy, MD, PhD; Thomas Stuart, RN, BSN; Alvin Perelman, MD

· Eight girls with central precocious puberty were treated with the long-acting gonadotropin releasing hormone analogue leuprolide acetate (Lupron) for a period of six to 18 months. Suppression of gonadotropin and estradiol secretion and regression of secondary sexual characteristics and menses were observed while patients received a subcutaneous dose of 35 to 40 µg/kg/d. Growth velocity was slowed in all but one patient, and the rate of skeletal maturation was slowed even more, resulting in a stabilization or improvement in predicted adult height. There were no major side effects. Although the long-term effects of leuprolide therapy cannot be determined with this study, it appears to be efficacious in the treatment of central precocious puberty.

(AJDC 1988;142:1061-1064)

Precocious puberty creates many problems. Development of secondary sexual characteristics is often embarrassing for the child and may cause difficulties at school or at home, leading to behavioral and school-related problems. Children with precocious puberty may also fail to reach an adult height in accordance with their genetic potential; this, too, may contribute to behavioral/social problems. For these reasons, attempts have been made over the years to treat children with precocious puberty using a variety of hormonal interventions, including medroxyprogesterone acetate, cyproterone acetate, and danazol. All these agents have proved to be unreliable and not efficacious.

Over the last ten years, analogues of gonadotropin releasing hormone (Gn-RH) that would function as inhibitors or superagonists of the natural hormone have been synthesized.1 These agents block the normal pulsatile secretion of Gn-RH and lead to suppressed secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Thus, the progression of central precocious puberty is interrupted. Mansfield et al2 and Comite et al³ reported their successful experience using the Gn-RH agonist D-Trp⁶-L-Pro⁹-NEt-Gn-RH for periods of six and 18 months. Other studies, using the same analogue4-6 or Bu-(D-Ser(tBu)6-GnRH-EA10),7 confirmed the success of superagonist therapy in the treatment of central precocious puberty.

The unavailability of these compounds led us to use a commercial Gn-RH analogue, leuprolide acetate (Lupron, TAP Pharmaceuticals, North Chicago, Ill), which is as efficacious as those previously reported. Leuprolide the D-Leu⁶, des Gly-NH₂¹⁰-Lproethylamide9 analogue of Gn-RH and has been used for several years with success in the treatment of prostatic carcinoma.8,9 This treatment resulted in an initial rise in the serum gonadotropin concentration and an increase in the serum testosterone concentration, but there was long-term suppression of testosterone secretion after the first 14 to 28 days of therapy.10 The drug was reported to have no serious adverse effects in humans or in animals, excepting atrophic changes in sex organs.11

PATIENTS AND METHODS

Eight girls were diagnosed as having central precocious puberty, as determined by the following criteria: (1) Tanner staging statistically in advance of normal limits for chronological age, (2) pubertal FSH/LH response to Gn-RH testing, (3) growth velocity increase more than 2 SDs for chronological age, and (4) skeletal maturation increase more than 2 SDs for chronological age. Only one patient failed to meet all criteria, and she fulfilled all but rapid growth velocity for age.

The study was conducted under IND No. 26,910 of the Food and Drug Administration, Public Health Service. Informed consent was obtained from the children and their parents in accordance with the institutional review boards of both hospitals. The children were seen every three months for interval history; physical examination, including assessment of height by stadiometer, weight, and Tanner stage; and laboratory examination, consisting of assessment of morning basal serum FSH, LH, and estradiol concentrations (means of two determinations taken 15 minutes apart). The Gn-RH tests were performed at some visits until prepubertal or no increase in FSH or LH above baseline was achieved. and occasionally afterward, and consisted of blood specimens being drawn at 0, 20, 40, 60, and 90 minutes after administration of an intravenous dose of Gn-RH (Factrel) 60 µg/m.2 Serum gonadotropin and estradiol concentrations were determined by radioimmunoassay at each institution using established commercial methods (Diagnostics Products Corp, Los Angeles), Roentgenograms to determine bone age were obtained every six months and were read by a single observer (M.S.K. and A.P.) at each institution.

Leuprolide acetate (D-Leu⁶, des Gly-NH₂¹⁰-L-Pro ethylamide⁹ analogue of Gn-RH) was administered by daily subcutaneous injection. Initial doses of less than 35 μg/kg proved to be ineffective in suppressing gonadotropin response to Gn-RH,

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and Phoenix Children's Hospital (Dr Perelman). Reprint requests to Children's Health Center of St Joseph's Hospital, 350 W Thomas, Phoenix, AZ 85013 (Dr Kappy).

| Clinical and Hormonal Characteristics of Eight Girls With Central Precocious Puberty* | | | | | | | | | | | | | |
|---|--------|--|----------------------|----------------|--------|---------------|---------|-------|---------------|--------|-----------|----------------------------|--|
| | | | Growth Rate, cm/y | Bone Age, y | Tanner | Stage | | | Level, I/L | LH Lev | rel, IU/L | Estradioi Level, pmol/l | |
| Patient No. | Age, y | Associated Diagnosis | | | Breast | Pubic Hair | Menses† | Basal | Peak‡ | Basal | Peak‡ | | |
| . 1 | 8.2 | Shunted hydrocephalus | 14.9 | 10.0 | 3-4 | 3-4 | + | 2.1 | 15.6 | 2.0 | 33.0 | 100 | |
| 2 | 6.8 | None | 18.0 | 8.8 | 2 | 1 | - | 3.6 | | 5.2 | 17.0 | <20 | |
| 3 | 4.8 | Seizure disorder | 13.1 | 7.8 | 3 | 2 | _ | 4.0 | 18.0 | 3.3 | 14.0 | <20 | |
| 4 | 6.6 | Meningomyelocele ventricular dilatation | 15.1 | 10.7 | 2-3 | 2-3 | + | 9.6 | 30.0 | 3.0 | 94.2 | 40 | |
| 5 | 9.3 | Arrested hydrocephalus | 8.0 | 11.5 | 2 | 2-3 | + | 3.2 | 39.0 | 0.2 | 156.8 | <20 | |
| 6 | 3.7 | None | 10.6 | 9.2 | 2 | 2 | - | 15.2 | 46.0 | 3.7 | 153.0 | 80 | |
| 7 | 8.0 | Quadrigeminal cyst shunted hydrocephalus | 10.8 | 10.5 | 3 | 3 | - | 2.7 | 18.9 | 5.8 | 58.4 | 60 | |
| 8 | 7.8 | Suprasellar cyst shunted hydrocephalus | 10.0 | 10.0 | 3 | 3 | *** | 4.4 | 12.0 | 9.2 | 26.0 | 30 | |

*FSH indicates follicle-stimulating hormone; LH, luteinizing hormone; and Gn-RH, gonadotropin releasing hormone.

and all patients, as of this writing, have been followed up for up to 18 months (mean, 11 months; range, six to 18 months) of suppressed gonadotrope function while receiving 35 to 40 μ g/kg/d.

Significance of differences between means was determined using Student's t test (two-tailed).

RESULTS

The Table shows the clinical and hormonal characteristics of the patients enrolled in this study. All but two of the girls had central nervous system abnormalities such as a seizure disorder of unknown origin, hydrocephalus, brain tumor, or cyst. All but one patient were under the age of 9 years, and all but one showed excessive growth velocity for age. They all had bone ages and Tanner stages that were significantly advanced for their chronological age. Patient 5 was first seen at age 9.3 years but had shown rapid growth for two years and breast and pubic hair development since the age of 7.8 years.

There was considerable variability in basal serum gonadotropin concentrations, but all girls showed at least threefold rises in serum FSH and LH concentrations after Gn-RH stimulation. Serum estradiol concentrations were elevated in only five patients, and there was no correlation between serum estradiol concentration and breast development. Three of the girls had a history of early menses before beginning therapy, and one other had

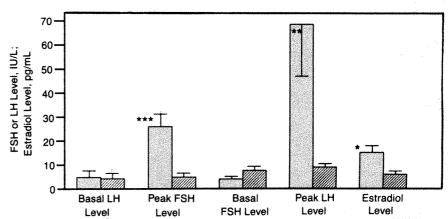


Fig 1.—Effect of treatment on basal serum gonadotropin and estradiol concentrations and on gonadotropin response to gonadotropin releasing hormone (Gn-RH) stimulation. Values are mean \pm SEM. Follicle-stimulating hormone (FSH) levels are given in international units per liter; luteinizing hormone levels, international units per liter; and estradiol levels, picograms per milliliter (to convert estradiol levels to picomoles per liter, multiply by 3.671). Open bar indicates pretreatment; hatched bar, during treatment; single asterisk, P<.05; double asterisk, P<.02; and triple asterisk, P<.01.

episodes of withdrawal bleeding within the first two weeks of hormonal therapy, which then resolved.

As shown in Fig 1, there were no significant differences in basal serum FSH or LH concentrations before or during therapy. Peak serum gonadotropin concentrations after Gn-RH stimulation fell significantly to levels that were statistically indistinguishable (P>.05) from basal levels. Thus, there was chemical evidence for suppression of gonadotropin secretion during therapy. This was usually obtained after two weeks of a regimen of daily doses of leuprolide acetate (35 to $40 \mu g/kg$). Serum estradiol concentra-

tions also fell significantly during therapy.

The effects of treatment on the patients' Tanner staging showed that an equal number of girls had an advance, no change, or regression in breast development. In contrast, the majority of girls showed either regression or no change in pubic hair, and menses ceased in the three girls with early menarche.

All but one of the girls showed a decrease in height velocity (Fig 2), and mean (\pm SEM) height velocity fell from 12.6 \pm 1.2 cm/y before treatment to 7.4 \pm 0.8 cm/y during treatment (P<.001). After one year of therapy,

[†]Plus sign indicates presence of menses; minus sign, absence of menses. Patient 6 experienced a withdrawal bleeding after the first two weeks of therapy, which then resolved.

[‡]Peak FSH and LH levels were measured following Gn-RH stimulation.

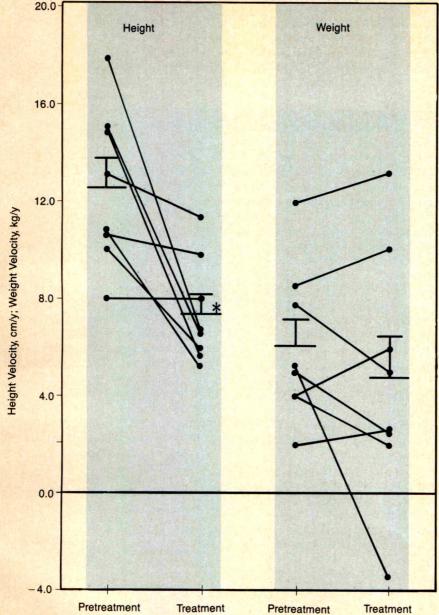


Fig 2.—Effect of treatment on growth and weight velocities. Horizontal lines indicate mean ± SEM. Asterisk indicates P<.001, treatment vs pretreatment.

one of the girls experienced a reduction in height velocity to below the normal limit for her bone age. The lowest posttreatment growth velocities were found in the older girls (r=-.81, P<.01) or in those with the most advanced bone age (r=-.82, P<.01) at diagnosis. The effect of treatment on weight gain was less consistent, but mean $(\pm \text{ SEM})$ weight velocity decreased slightly, but not significantly, from 6.1 ± 1.1 kg/y to 4.8 ± 1.7 kg/y during therapy.

A mean (± SEM) ratio of change in bone age to change in chronological age $(\Delta BA-\Delta CA)$ of 1.49 ± 0.15 was found prior to the institution of therapy and decreased during therapy to a mean value of 0.84 ± 0.11 (P<.001). Mean pretreatment change in bone age to change in height age $\Delta BA-\Delta HA$ ratio was 1.30 ± 0.12 , and decreased to 0.72 ± 0.11 during treatment (P<.001).

The predicted final heights of all girls when first seen, which were estimated using the tables of Bayley and Pinneau, were already significantly less than expected, as based on their mid-parent stature (data not shown).

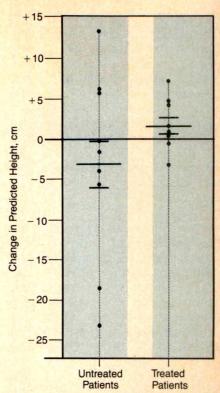


Fig 3.—Change in predicted height from date of diagnosis. Data on untreated girls were calculated from report of Sigurjons-dottir and Hayles. 13 Horizontal lines indicate mean ± SEM.

Furthermore, all but one of the girls had initial predicted heights that were even less than those of their mothers. After 18 months or less of treatment, all but two of the girls had predicted final heights that were within 1 cm of their initial prediction or were gains of up to 8 cm (Fig 3). Only one girl showed a decrease in predicted height of more than 2 cm. She was the patient who showed the most rapid weight gain during the course of therapy, such that maintenance of a suppressive dose of leuprolide was difficult; this may have prevented her from realizing the full effects of therapy.

Comparative data on ten untreated patients who had reached adult height were taken from the study of Sigurjonsdottir and Hayles. This study was used as a source of information on untreated patients, and is one of the only published studies where early height predictions based on bone age were compared with final heights. The changes in predicted height for these girls were quite variable, as shown in Fig 3. Although there was a mean loss

of 3.2 cm in the untreated group, compared with a mean gain of 2.0 cm for our treated group, the difference was not statistically significant.

Side effects reported by patients included a mild, intermittent rash for a two-week period, which disappeared when simultaneously administered antibiotic therapy was discontinued. In addition, one patient reported occasional hot flashes during therapy with leuprolide.

COMMENT

Our study demonstrates the effectiveness of leuprolide therapy in the treatment of central precocious puberty in girls. Although the percentage of patients with central nervous system abnormalities was higher in the present study than in the much larger National Institutes of Health, Bethesda, Md, study, there were no significant differences in responses to therapy between children with idiopathic precocity and those who had central nervous system abnormalities.

Suppression of gonadotrope function was evidenced by a marked decrease in peak serum FSH and LH concentrations after Gn-RH stimulation. Changes in basal serum FSH and LH concentrations or in serum estradiol concentrations were not as significant, suggesting that Gn-RH testing is necessary to monitor hormonal responses to therapy. Two girls in our study who decided to discontinue leuprolide therapy had a prompt return

of Gn-RH-stimulated serum FSH and LH concentrations into the pubertal range.

The absence of pubertal serum estradiol concentrations in some of the girls who showed estrogen effect on physical examination is similar to that reported by Boepple et ale and may be due to cyclical estrogen secretion, and/ or relative lack of ability on the part of the physician to distinguish between prepubertal and mildly elevated serum estradiol concentrations using current radioimmunoassay methods. Nevertheless, signs of estrogen stimulation, such as breast development, either regressed or did not advance in the majority of our patients. In another study, vaginal cytologic studies also showed a return to a less-stimulated appearance during therapy.6

Marked decreases in height velocity with the current treatment regimen were also observed in all but one of our patients. Although the height velocity fell below the normal range for bone age in one of the girls, her serum somatomedin-C concentration and thyroid function remained normal. For most of the girls, the slowdown in skeletal maturation was more pronounced than that in height velocity, resulting in a stabilization or increase in predicted adult height, although the effects of leuprolide therapy on our patients' adult heights will not be known until they have reached maturity.

The effective dose of leuprolide ac-

etate in the present study was approximately 35 to 40 µg/kg/d. This is higher than that reported for other analogues2-7 but is in keeping with the Gn-RH analogue potency studies reported by Boeppel et al.6 The most frequently used Gn-RH analogue, D-Trp⁶-Pro⁹-NEt-Gn-RH, has a potency approximately 144 times that of the natural hormone, whereas the analogue that is the equivalent of leuprolide was reportedly only 12 to 20 times as potent as Gn-RH. Thus, one might have expected a sevenfold to tenfold increase in dosage requirement when using leuprolide, and this was the case. This resulted in a daily dosage of 1.0 to 1.5 mg for our patients.

Thus, leuprolide therapy meets the goals of successful treatment of precocious puberty by suppressing gonadal sex-steroid secretion, slowing the progression or causing a regression of secondary sexual characteristics, and slowing skeletal maturation more than growth so that estimated final height may be increased. We have seen an absence of major toxicity during relatively long-term administration of leuprolide, with return of gonadarche after treatment is discontinued.

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Recurrence Risk of Neonatal Hyperbilirubinemia in Siblings

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• The recurrence of neonatal hyperbilirubinemia (NHB) in full siblings was studied in 3301 live infants born between 1966 and 1986 to 1669 male US Army veterans who were part of a nationwide health study. The study population included 580 sibships with one infant, 679 with two, and 410 with three or more. Hospital of birth medical records were abstracted on these children. Neonatal hyperbilirubinemia was defined as present if the recorded peak bilirubin level was greater than 205 µmol/L in the absence of hemolytic disease of the newborn. The risk of NHB in newborns who have one or more prior sibs with NHB was 3.1 times higher than that of newborns who have prior sibs without NHB (10.3% vs 3.6%). Simultaneous adjustment for risk factors for NHB, such as feeding patterns, year of birth, maternal obstetric events, and infant health variables, did not explain the excess risk of NHB in sibs. Moreover, the risk of severe NHB (peak bilirubin level, >257 μmol/L) in newborns who have one or more prior sibs with severe NHB was 12.5 times higher than that of newborns who have prior sibs without severe NHB (10.5% vs 0.9%). Separate analyses in sibships where all sibs were breast-fed and in sibships where all sibs were bottle-fed gave similar results. These data clearly suggest the familial nature of NHB. The higher risk of recurrence of NHB in sibs does not seem to be due to known environmental risk factors for NHB.

(AJDC 1988;142:1065-1069)

Hyperbilirubinemia is one of the most common medical problems occurring during the neonatal period. While some jaundice is almost a universal occurrence in neonates and is benign, 5% to 20% of infants have been described with peak bilirubin

levels exceeding 205 µmol/L, and 0.5% to 5% of infants may have peak bilirubin levels exceeding 257 µmol/L,2-4 possibly requiring therapeutic intervention. The pathogenesis of neonatal hyperbilirubinemia (NHB) is complex and may involve multiple pathways in bilirubin metabolism.5 The causes of NHB are also varied and may involve the interrelationship of multiple factors. Some of the "risk factors" that have been associated with increased occurrence of NHB include race/ethnicity,6-9 prematurity and low birth weight, 10,11 epidural anesthesia, 11,12 labor induction,12 male gender,11 breastfeeding,3,4 infections,10 and neonatal weight loss.2,12

While numerous studies have investigated the relationship between obstetric and early neonatal factors and the occurrence of NHB, little is known about the role of genetic factors. Several hemolytic diseases of the newborn have known mendelian patterns of inheritance, including blood group alloimmunization disorders (eg, Rh incompatibility), erythrocyte biochemical defects (eg, pyruvate kinase deficiency), and erythrocyte structural abnormalities (eg, hereditary spherocytosis).5 Also, a few nonhemolytic disorders associated with NHB have a mendelian basis, such as Criggler-Najjar, Gilbert's, and Dubin-Johnson syndromes.5 Moreover, a few familial cases of severe transient NHB have been reported by Lucey et al13 and Arias et al.¹⁴ Except for possibly Gilbert's syndrome, these nonhemolytic disorders are quite rare and can account for only a small proportion of NHB cases. More recently, in a study of 422 full siblings born in two Danish hospitals, Nielsen et al15 found a highly significant correlation in peak bilirubin levels between siblings, which was independent of the presence of known risk factors for NHB, such as breastfeeding and gestational age. To our knowledge, no systematic populationbased survey of the recurrence risk of idiopathic NHB among siblings has been conducted in the United States.

In this study, we investigated the

recurrence risk of neonatal hyperbilirubinemia (peak bilirubin level, >205µmol/L) and severe NHB (peak bilirubin level, >257 µmol/L) in 1669 sibships with 3301 neonates who were part of a nationwide health study of the reproductive outcomes of male US Army veterans. After excluding cases of hemolytic disease due to blood group incompatibility, we documented a strong familial component in NHB and severe NHB that was independent of the effects of known environmental risk factors for NHB.

PATIENTS AND METHODS Study Population

Infants in this study were offspring of 1669 male US Army veterans who entered the Army between 1965 and 1971 and who participated in a nationwide study of veterans' health. Details of the study design and data collection are published elsewhere.16 During the medical interview, participants were asked about all of the liveborn and stillborn infants they had conceived. For each child, the interviewer obtained the child's full name, date of birth, name and location of birth hospital, mother's maiden name, and mother's name at the time of birth. Written authorization was obtained from each man to access hospital newborn medical records of all children under the age of 18 years. Fewer than 1.5% of all men refused to participate in this study. Photocopies of hospital newborn records were obtained for nearly 92% of the children. All children in the study were born between 1966 and 1986, inclu-

Medical Record Abstraction

Trained staff from the Centers for Disease Control, Atlanta, abstracted and coded relevant medical information from newborn records, including the following: (1) maternal information: age, gravidity, parity, education, marital status, prenatal events, labor and delivery complications, method of delivery, use and type of obstetric anesthesia; and (2) child information: final diagnosis, Apgar score at one and five minutes, birth weight, newborn anthropometric measurements, gestational age (primarily derived using information from the date of the first day of the last menstrual period; when such information was missing, the gestational age recorded by the attending physician was considered), presence

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| Table 1.—Sibship Size Distribution of the Study Population | | | | | |
|--|-------------------------------|---------------------------------|--|--|--|
| Sibship | No. of | No. of | | | |
| Size | Sibships | Siblings | | | |
| 1 2 3 4 5 5 | 580 679 308 79 18 | 580 1358 924 316 90 | | | |
| 7 | 3 | 21 | | | |
| Total | 1669 | 3301 | | | |

and types of congenital malformations, complications and medical conditions during hospitalization, presence of neonatal jaundice, highest observed bilirubin level, status at discharge, and date of discharge. All medical conditions were coded by a trained staff member using the *International Classification of Diseases*, ninth revision.¹⁷

Sibship Reconstruction

Of 3495 infants considered for this analysis, we excluded 92 infants who had a different mother's name from the rest of the sibship (paternal half sibs), 34 infants who were members of a twin delivery (in the event of a twin birth, only one of the infants was randomly included in the analysis), 18 stillbirths, and 50 infants whose records showed evidence of hemolytic disease of the newborn due to blood group incompatibility or other hereditary hemolytic disorders (International Classification of Diseases, ninth revision, codes: 773-774.1).

The final sample of eligible infants for the analysis (3301 neonates) was arranged into sibships by sorting the records by the father's unique identification number and chronologically by the date of birth. As shown in Table 1, the 3301 infants were part of 1669 sibships. There were 580 sibships with one infant in this analysis and 1089 sibships with two or more siblings (with a maximum size of seven siblings).

Definition of Outcome Variables

In this analysis, we defined NHB by the presence of the highest observed bilirubin level exceeding 205 µmol/L. For the analysis of sibling recurrence of NHB by severity of jaundice, we further defined the three following levels of jaundice: (1) mild if jaundice was noted in the record and/or highest bilirubin level was 205 µmol/L or less, (2) intermediate if highest bilirubin level was between 205 µmol/L and 257 µmol/L, and (3) severe if the highest bilirubin level exceeded 257 µmol/L.

Statistical Analysis

To address the question of recurrence of NHB among siblings, we compared the rate

Table 2.—Number and Rate (per 100) of Neonatal Hyperbilirubinemia (NHB) by Selected Maternal and Infant Characteristics

| Factor | No. of Neonates | Rate, % | No. With NHB | Crude Odds Ratio | 95% Confidence Intervals |
|-------------------------------------|--------------------|--------------|-----------------|------------------------|--------------------------------|
| Gestational age, wk/birth weight, g | | | | | |
| ≥37/>2500 g | 2292 | 4.36 | 100 | 1.00 | 0.70 5.66 |
| ≥37/<2500 g | 48 | 8.33 9.22 | 4 | 1.99 | 0.70-5.66 1.33-3.72 |
| <37 Not recorded | 206 755 | 3.18 | 19 24 | 2.23* 0.72 | 0.45-1.15 |
| Race | 733 | 3, 16 | 24 | U.1 & | 0.40-1.10 |
| White | 2343 | 4.61 | 108 | 1.00 | • • • |
| Black | 231 | 1.73 | 4 | 0.37* | 0.13-1.00 |
| Other | 81 | 6.17 | 5 | 1.36 | 0.54-3.43 |
| Not recorded | 646 | 4.64 | 30 | 1.01 | 0.67-1.53 |
| Sex | 1670 | 4 70 | 00 | 1 17 | 0.00 1.63 |
| M F | 1673 1627 | 4.78 4.12 | 80 67 | 1.17 1.00 | 0.89-1.63 |
| Plurality | 1021 | 4.12 | 67 | 1.00 | ••• |
| Singleton | 3266 | 4.41 | 144 | 1.00 | • • • |
| Twin | 35 | 8.57 | 3 | 2.03 | 0.62-6.72 |
| Year of birth | | | ,_ | | |
| 1966-1970 | 441 | 3.85 | 17 | 1.00 | 3er 1 |
| 1971-1975 | 1228 | 3.09 | 38 | 0.80 | 0.45-1.43 |
| 1976-1980 | 1088 | 5.61 | 61 | 1.48 1.51 | 0.86-2.57 |
| 1981-1986 | 544 | 5.70 | 31 | 1.51 | 0.82-2.76 |
| Type of delivery Vaginal | 2451 | 4.45 | 109 | 1.00 | |
| Cesarean section | 368 | 5.98 | 22 | 1.34 | 0.84-2.15 |
| Not recorded | 482 | 3.32 | 16 | 0.74 | 0.43-1.26 |
| Maternal age, y | | | | | |
| <14 | 1123 | 4.19 | 47 | 1.00 | |
| 15-29 | 873 | 4.47 | 39 | 1.07 | 0.69-1.65 |
| 30-34 | 412 | 6.55 | 27 | 1.61 | 0.99-2.61 |
| ≥35 | 78 | 5.13 | 4 | 1.24 | 0.43-3.53 |
| Not recorded | 815 | 3.68 | 30 | 0.88 | 0.55-1.40 |
| Gravidity 1 | 973 | 5.55 | 54 | 1.00 | |
| 2 | 964 | 3.94 | 38 | 0.70 | 0.46-1.07 |
| ≥3 | 885 | 4.63 | 41 | 0.83 | 0.55-1.25 |
| Not recorded | 479 | 2.92 | 14 | 0.51* | 0.28-0.93 |
| Anesthesia | | | | | |
| Local/none | 899 | 5.67 | 51 | 1.00 | |
| Epidural | 187 | 4.28 | 8 | 0.73 | 0.32-1.64 |
| Spinal | 547 | 5.67 | 31 | 1.00 | 0.61-1.62 |
| General Other/not recorded | 293 | 4.10 | 12 45 | 0.71 0.56* | 0.35-1.40 |
| Other/not recorded | 1375 | 3.27 | 45 | ∪.ე ნ ″ | 0.37-0.86 |
| Feeding Bottle | 1685 | 3.20 | 54 | 1.00 | • • • |
| Breast | 1124 | 6.49 | 73 | 2.10* | 1.46-3.01 |
| Other/not recorded | 492 | 4.07 | 20 | 1.28 | 0.76-2.16 |
| Apgar score at 1 minute | | | | | |
| <7 | 226 | 7.96 | 18 | 1.86* | 1.11-3.13 |
| 7-10 | 2501 | 4.44 | 111 | 1.00 | 0.42-1-16 |
| Not recorded | 574 | 3.14 | 18 | 0.70 | 0.42-1.16 |

^{*}P<.05.

of NHB in children who had one or more previous sibs with NHB with the rate of NHB in children who had previous sibs with no NHB. Odds ratios (ORs) and 95% confidence intervals were computed using the Statistical Analysis System package. ¹⁸ We considered analyzing the number of prior sibs with NHB for sibships of three or more, but there were only two infants who had two prior sibs with NHB. There-

Table 3.—Recurrence Risks of Neonatal Hyperbilirubinemia (NHB) Among Sibs, by Status of Prior Sibs

| Child Order | Status of Prior Sibs | N | Risk of NHB, % (No.) of Patients | Odds Ratio (Confidence Interval) |
|----------------|-------------------------|------|-------------------------------------|-------------------------------------|
| | | 1669 | 4.97 (83) | () |
| | No NHB | 1545 | 3.56 (55) | 1.00 () |
| ≥2 | >1 NHB | 87 | 10.34 (9) | 3.13*(1.39-6.84) |

^{*}P<.01.

Table 4.—Result of Modified Conditional Logistic Regression Analysis of Factors
Affecting Risk of Neonatal Hyperbilirubinemia

| Variable* | Adjusted Odds Ratio | 95% Confidence Interval |
|--|------------------------|-------------------------------|
| Sibling pairwise odds ratio | 2.37† | 1.18-4.74 |
| Year of birth ≤1975 | 1.00 | |
| >1975 | 1.49† | 1.03-2.15 |
| Gestational age, wk/birth weight, g ≥37/≥2500 g | 1.00 | |
| ≥37/<2500 g | 1.93 | 0.66-5.62 |
| <37 | 2.37† | 1.42-3.94 |
| Not recorded | 0.83 | 0.52-1.32 |
| Type of feeding Bottle | 1.00 | |
| Breast | 1.85† | 1.27-2.71 |
| Other | 1.18 | 0.70-1.99 |
| Neonatal asphyxia 1-minute Apgar score, 7-10 | 1.00 | |
| 1-minute Apgar score, <7 | 1.69 | 0.99-2.89 |
| Not recorded | 0.91 | 0.52-1.59 |

^{*}Other variables considered were plurality, race, maternal age, gravidity, and type of delivery. †P<.05.

fore, no meaningful analysis could be done with these sibships.

To examine whether the familial risk of NHB is independent of other known risk factors for NHB, it was important to consider several factors that can act as potential confounders by recurring in sibships. For example, if mothers tend to breastfeed the second child if the first child was breast-fed, then breast-feeding could account for the apparent excess of NHB in siblings. Other potentially confounding factors considered in the analysis were race (white, black, other), sex (male, female), plurality (single, twin), gestational age/birth weight (≥37 wk/≥2500 g, <37wk/ \geq 2500 g, and <37 wk/<2500 g), year of birth (five-year intervals), maternal age (five-year intervals), gravidity (1,2, and 3+), type of delivery (vaginal, cesarean section), obstetric anesthesia (local, epidural, spinal, general), and neonatal asphyxia (Apgar score at one minute, <7, 7

To simultaneously consider familial risk in addition to other factors in predicting

the risk of NHB, the standard logistic regression analysis could not be used because it relies on the assumption of independence for outcomes between individuals -an assumption that is violated by correlated sibship data. Instead, we used a modified logistic regression model proposed by Connolly and Liang19 that takes into account the independence problem. This model uses in its logistic form a conditional probability function for each child in a family given the number of positive outcomes in the remaining children. Because the logistic form is defined as a conditional probability function within a family, the independence assumption is not required. The model yields a sibling pairwise OR-the ratio of the odds of NHB in a child given that the prior sib had NHB over the odds of NHB in a child given that the prior sib did not have NHB. Also, the pairwise OR using this model takes into account differences in family size that may explain apparent increases of the number of affected infants in sibships with increasing sibship size.

RESULTS Factors Affecting the Risk of NHB In the Study Population

The rate of NHB in the entire newborn population was 4.5% (147/3301). Table 2 shows the results of the unadjusted analyses of maternal and infant variables associated with the rate of NHB in the study population. Several factors were significantly associated with variation in the risk of NHB. These included prematurity (<37 weeks, OR = 2.23), black race (OR = 0.37), breast-feeding (OR = 2.10), and neonatal asphyxia (Apgar score at one minute, <7; OR = 1.86). For other factors, there was a suggestive (but not statistically significant) association with the risk of NHB. These included small for gestational age (>37 weeks and <2500 g, OR = 1.99), twin delivery (OR = 2.03), year of birth (1976 to 1980, OR = 1.48; 1981 and beyond, OR = 1.51), and maternal age (30 to 34 years, OR = 1.61).

Unadjusted Sibling Recurrence Risk of NHB

Table 3 shows the rate of NHB by sib order and NHB status of prior sibs. The rate of NHB in the first child of a sibship was 4.97% (83/1669). Among second- or higher-order children, the risk of NHB was 3.13 times higher among those who had one or more prior sibs with NHB compared with those who had prior sibs with no NHB (10.34% vs 3.56%, P<.05). There were only two children who had two affected prior sibs; one of them had NHB (recurrence risk, 50.0%).

Results of Logistic Regression Analysis

Table 4 shows results of the modified logistic regression analysis that simultaneously considers multiple factors associated with the risk of NHB in addition to the sib pairwise OR. The final variables that remained predictive of NHB in the model were year of birth (after 1975 vs 1975 or before, adjusted OR = 1.49), prematurity (<37weeks, adjusted OR = 2.37), breastfeeding (adjusted OR = 1.85), and neonatal asphyxia (Apgar score at one minute, <7; adjusted OR = 1.69). In addition, the sib pairwise OR remained significant in the model. Newborns who had a prior sib with NHB

were found to be 2.37 times more likely to have NHB compared with newborns who had a prior sib without NHB (95% confidence intervals, 1.18 to 4.74).

Sib Recurrence of NHB in Breast-fed and Bottle-fed Sibships

To further examine the relationship of breast-feeding with the recurrence of NHB in sibs, we examined the risk of NHB separately in sibships where all children were breast-fed and in sibships where all children were bottle-fed. As shown in Table 5, in breastfed sibships, newborns with prior sibs with NHB were 3.43 times more likely to have NHB than were newborns whose prior sibs did not have NHB (15.63% vs 5.12%, P < .05). Also, among bottle-fed sibships, newborns who had one or more prior sibs with NHB were 3.74 times more likely to have NHB than were newborns who had prior sibs with no NHB (11.76% vs 3.44%). This latter difference was not statistically significant at the .05 level.

Sibling Recurrence of NHB by Level of Jaundice

Table 6 shows sibling recurrence risks by level of jaundice. A clear trend of increasing sibling risk with increasing severity of hyperbilirubinemia was observed. When severe NHB was examined (bilirubin level. >257 µmol/L), newborns with prior sibs with severe NHB were 12.5 times more likely to have severe NHB compared with newborns who had prior sibs without severe NHB (10.5% vs 0.9%). For moderate jaundice (bilirubin levels between 205 µmol/L and 257 µmol/L), the sibling OR was 4.10 (8.82% vs 2.30%), while for mild jaundice (bilirubin level, ≤205 µmol/L), the sibling OR was 2.72 (25.30% vs 11.09%).

COMMENT

The main findings of this nationwide newborn survey are (1) that the recurrence risk of NHB is increased in full sibs of infants with NHB compared with full sibs of infants without NHB; (2) that the excess risk of NHB in siblings is independent of the effect of known risk factors for NHB, such as breast-feeding, prematurity, and other maternal and infant characteristics, that may recur in sibships; (3) that the

Table 5.—Sib Recurrence Risks of Neonatal Hyperbilirubinemia (NHB) Among Breast-fed and Bottle-fed Sibs

| OF 11-4 | All Siblings Breast-fed* | | All Siblings Bottle-fed* | | | Bottle-fed* | | | |
|---------|--------------------------|-----|--------------------------|-----|-------------------|-------------|-------|-----|------------------|
| | Prior Sibs | N | % | No. | OR (95% CI) | N | % | No. | OR (95% CI) |
| 1 | | 701 | 6.85 | 48 | | 1058 | 2.93 | 31 | |
| -0 | No NHB | 391 | 5.12 | 20 | 1.00 | 610 | 3.44 | 21 | 1.00 |
| =2 { | 1 + NHB | 32 | 15.63 | 5 | 3.43† (1.04-10.7) | 17 | 11.76 | 2 | 3.74 (0.39-18.9) |

^{*}OR indicates odds ratio; CI, confidence interval. †P<.05.

| | | | | High | est Bi | irubi | n Level, μn | nol/L* | | |
|----------------|------------------------------|------|-------|----------------|--------|-------|----------------|--------|------|----------------|
| | Peak of | | ≤20 | 205 205-257 | | | >257 | | | |
| Child Order | Peak of Prior Siblings | N | % | OR (95% CI) | N | % | OR (95% CI) | N | % | OR (95% CI) |
| 1 | | 1669 | 8.15 | | 1669 | 3.65 | * * * | 1669 | 1.32 | · · · |
| ſN | lo NHB | 1380 | 11.09 | 1.0 | 1380 | 2.30 | 1.0 | 1389 | 0.94 | 1.0 |

68 8.82

4.10†

(1.48-10.8)

2.72†

(1.81-4.07)

166 25.30

1 + NHB

(same range)

excess risk of NHB in sibs is most notable for severe neonatal jaundice (peak bilirubin level, >257 μ mol/L) and least notable for mild jaundice (peak bilirubin level, \leq 205 μ mol/L); and (4) that the excess risk of NHB in siblings is not consistent with a simple mendelian basis (about 10% to 15% recurrence risks).

Before discussing the implications of these findings, it is important to consider the study's strengths and limitations. First, newborns in this study were part of a larger study of the reproductive outcomes and health of children of male US Army veterans. 16 How representative is this sample of US newborns in general, and can the findings found here be generalized to other newborn populations? While replication of the study in other populations is desirable to test the consistency of our findings, we believe that our sample is suitable to study NHB and that it is not biased in any systematic fashion for several reasons: (1) the rates of NHB found here are similar to those reported in other newborn populations¹⁻⁴ and seem to reflect an increase over times; and (2) several risk factors for NHB found in other populations were also documented in

this sample, notably gestational age and breast-feeding. On the contrary, we believe that the study population has some unique advantages: (1) the sample is nationwide and derived from a mixture of hospitals (rural, urban, primary, tertiary, community, and teaching) and results from different hospitals and geographic locations were similar; and (2) the sample covers a period of 21 years during which time obstetric and neonatal practices have undergone numerous changes, including earlier hospital discharge of newborns. That the sib recurrence in NHB is found despite these variations adds further strength to the findings.

12.5†

(2.29-65.3)

19 10.53

Second, data on the presence of neonatal jaundice were collected retrospectively by reviewing newborn medical records. The laboratory methods of bilirubin measurements and quality control procedures were probably different among different hospitals and certainly cannot be evaluated here. Such variation is unlikely to have introduced a systematic bias in our findings.

Third, could our findings be attributed to detection bias? For example, if the first child of a sibship had high bilirubin levels that necessitated ther-

^{*}OR indicates odds ratio; CI, confidence interval. †P<.01.

apeutic intervention, such as phototherapy, parents and physicians may look more closely for jaundice in a subsequent child, leading to closer monitoring of bilirubin levels and detection of NHB that may have gone otherwise undetected. However, while detection bias could operate in instances of mild jaundice (bilirubin level, <205 µmol/L), it is unlikely to operate when the bilirubin level is above 205 µmol/L, and less so if the level is more than 257 µmol/L. The fact that we found a stronger sib recurrence risk of NHB with more severe jaundice argues against the effects of detection bias in this study.

The excess risk of neonatal hyperbilirubinemia found in this study is consistent with the high correlation in bilirubin levels in sibs found by Nielsen et al¹⁵ in Denmark. Consistent with the study by Nielsen et al is the inability of obstetric and infant variables to account for the familial association. One apparent discrepancy is that breast-feeding was associated with a decrease in bilirubin levels in the study by Nielsen et al, a finding at odds with those in this study and the literature. At

The familial nature of NHB may be due to a combination of genetic and environmental factors. Although the known environmental risk factors for NHB could not explain the excess risk. unmeasured environmental factors not documented in previous investigations of NHB could be operating. It would be difficult on the basis of the data presented herein and those of Nielsen et al¹⁵ to conclude that the familial nature of NHB can be explained exclusively on the basis of genetic factors. The potential role of environmental factors was suggested by Drew and Kitchen,7 who found a decline in the incidence of NHB in Greek migrants who had moved from high-risk to low-risk areas.

Familial and genetic factors could be operating in the pathogenesis of NHB along one or more pathways of bilirubin metabolism. First, hyperbilirubinemia can occur because of an increased load of bilirubin due to increased red blood cell load or turnover (half-life, hemolysis, structural abnormalities, or sequestered blood). While hemolytic diseases such as Rh and ABO blood group incompatibility have

been ruled out in this study, familial factors may still be involved at this stage. For example, increased bilirubin production has been suggested recently to partially explain the excess risk of NHB in Navajo neonates.³

Second, familial factors could be operating via effects on the conjugation and/or transport of bilirubin. Conjugation is affected by a reduction of the activity of hepatic glucuronyl transferase (GT) enzyme. The wellknown autosomal recessive Criggler-Najjar syndrome (type I) is associated with complete absence of the enzyme and is too rare to account for familial clustering in such a sample of neonates. On the other hand, reduced hepatic GT is also seen with the milder form of the Criggler-Najjar syndrome (type II) and with Gilbert's syndrome. The latter entity may be a rather common autosomal dominant disorder, affecting up to 6% of the normal population.5 Although it has been suggested that neonatal jaundice may be an early manifestation of Gilbert's syndrome, this has not been documented in large-scale studies. Further studies need to document the magnitude of this entity in the population and to assess whether it can explain the familial nature of NHB. Moreover, familial factors could affect the transport of bilirubin. A decrease in the activity of hepatic glutathione-S transferase-B (ligandin) can lead to unconjugated hyperbilirubinemia. 5 To our knowledge, no genetic syndromes have been associated with abnormalities in this enzyme.

Third, familial factors could be operating via the enterohepatic circulation of bilirubin. The role of enterohepatic circulation recently has received increasing attention as an important mechanism of breast milk jaundice. 5,20 Factors leading to an increase in bilirubin enterohepatic transport, such as with intestinal obstruction, can certainly contribute to NHB.

Last, the pathogenesis of NHB is often multifactorial, with contributions from one or more pathways of bilirubin metabolism (such as NHB seen with prematurity and infections).⁵

In conclusion, the findings of this study document the familial nature of NHB that is present regardless of breast-feeding and other risk factors. It is hoped that future studies will investigate more closely the pathogenetic mechanisms in bilirubin metabolism that are responsible for the excess familial risk. Such work potentially can lead to better delineation of the multifactorial nature of NHB and to the application of effective intervention strategies.

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Plasma Prorenin and Renin in Childhood and Adolescence

Darrell M. Wilson, MD; David K. Stevenson, MD; John A. Luetscher, MD

 We studied 108 subjects (age range, 4 to 76 years) to determine the effect of age on prorenin (inactive renin), active renin, and plasma renin activity in normal children, adolescents, and adults. Children and adolescents had lower prorenin concentrations and higher plasma renin activity and active renin concentrations than did adults. Prorenin concentrations were positively correlated with age over the range of 4 to 76 years, while plasma renin activity and active renin concentration were negatively correlated with age. Plasma prorenin and active renin concentrations from umbilical cord blood samples obtained from 11 newborns and arterial samples obtained from five infants were higher than those in samples obtained from children or adults.

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Renin plays an important role in the maintenance of body sodium, plasma volume, and blood pressure in children.¹ Plasma renin acts by enzymatically cleaving angiotensinogen to angiotensin I (AI). Angiotensin I is rapidly converted to angiotensin II, which acts as a vasoconstrictor and a stimulus to aldosterone production in the adrenal cortex. Renin, secreted into the blood by juxtaglomerular cells of the kidneys, is derived from a larger precursor. This precursor, initially called big renin or inactive renin, is now referred to as prorenin.²⁴

Prorenin is present in the plasma of normal adults in a concentration five to ten times greater than that of active renin.⁵ The plasma prorenin concentration is elevated in certain pathologic conditions. Diabetic adults with microvascular complications have increased levels of plasma prorenin.⁶ A large, inactive renin was characterized in plasma and extracts of a reninsecreting Wilms' tumor removed from a hypertensive child.² The purpose of this study is to define the normal ranges of plasma prorenin, as well as plasma renin activity (PRA) and active renin (renin activity using sheep angiotensinogen as the substrate), in newborns, normal children, and adolescents.

SUBJECTS AND METHODS

Plasma renin activity and concentrations of active renin and prorenin were measured enzymatically in 50 healthy children and adolescents (age range, 4 to 17 years) seen in a pediatric clinic. Twenty-eight subjects were being seen for a routine health check, ten subjects for follow-up of hyperthyroidism or hypothyroidism (treated and currently euthyroid), ten subjects for normal variant short stature, and two subjects for idiopathic precocious sexual development. Blood was drawn only when venipuncture was required for clinical reasons. Active renin and prorenin concentrations were also measured in umbilical cord blood samples from 11 normal newborns (gestational ages, 36 to 40 weeks; birth weights, 1.9 to 4 kg) and in plasma obtained from the umbilical arterial catheters of five infants, 1 to 2 days of age. These five infants (gestational ages, 37 to 41 weeks; birth

weights, 3 to 4.1 kg) had been admitted to the neonatal intensive care unit in mild to moderate distress and were judged to be clinically stable at the time the samples were obtained. Plasma samples from 58 healthy adults (age range, 19 to 76 years) were also assayed to compare with the results from the children. All subjects were normotensive on an unrestricted diet, were not taking any medications affecting the plasma renin concentration, and had normal renal function. Samples were obtained between 10 AM and 4 PM with no restriction on activity. These studies were approved by the Stanford Committee for the Protection of Experimental Subjects.

Blood was collected in tubes containing ethylenediaminetetraacetic acid and promptly centrifuged. Plasma was separated, frozen, and stored at -20°C. Assays have been described elsewhere.6 In brief, PRA represents the rate of formation of AI in plasma incubated at 37°C and pH 7.4 at 37°C, expressed as nanograms of AI per liter-second (to convert to nanograms of AI per milliliter-hour, multiply by 3.6). Active renin concentration was measured using added sheep angiotensinogen as the substrate. To determine the total renin concentration, an identical aliquot of plasma was dialyzed first to a pH of 3.3 and then to a pH of 7.4 to activate prorenin. The plasma prorenin concentration was calculated by subtracting the active concentration from the total renin concentration. The interassay variation of these assays is 7%, judged by internal controls run with each assay. As the volume of blood drawn from infants

and Prorenin in Infants, Children, Adolescents, and Adults*

| Group | No. of Cases | Age, y | PRA | Active Renin, ng of Al/L·s | Prorenin, ng of Al/L•s |
|---|--------------|---------|--------------|-------------------------------|---------------------------|
| Newborns (umbilical cord blood samples) | 11 | | | 10.00 ± 7.06† | 15.83 ± 3.49† |
| Infants | 5 | | | 9.04 ± 6.84† | 37.50 ± 29.52† |
| Children | 11 | 5 ± 2 | 0.46 ± 0.24† | 2.52 ± 1.20† | 6.82 ± 3.32† |
| Adolescent | 30 | 14±2 | 0.36 ± 0.21† | 2.05 ± 1.24† | 6.69 ± 2.52† |
| Adults | 58 | 41 ± 15 | 0.20 ± 0.16 | 1.12 ± 0.79 | 8.97 ± 3.87 |

Plasma Renin Activity and Plasma Concentrations of Active Renin

*Children ranged in age from 4 to 9 years; adolescents, 10 to 17 years; and adults, 18 years or older. Values are expressed as the mean ± SD. PRA indicates plasma renin activity; AI, angiotensin I. (To convert from nanograms of AI per liter-second to nanograms of AI per milliliter-hour, multiply by 3.6.) †P<.05 when compared with adult concentrations.

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was too small to permit dialysis, prorenin was activated by adding trypsin, 1 mg/mL, to the plasma at -4° C; after ten minutes, an equal quantity of lima bean trypsin inhibitor was added. This method gives total renin results very similar to those after acid dialysis. 5 Since other laboratories may use different activation conditions or assays, reference to an international standard is desirable. In this laboratory, 1 microinternational unit of standard renin provided by the National Institute for Biological Standards and Control (Holly Hill, Hampstead, London) generates 0.061 ng of AI per liter-second from sheep angiotensinogen.

Mean plasma concentrations from the different age groups were compared by using t tests. Associations between variables were determined using Pearson's correlation method. Probability (P) values of less than .05 were considered significant.

RESULTS Plasma Renin Activity

Mean PRA was significantly higher in children and adolescents than in adults (Table). Although there was considerable overlap in the ranges for different age groups, values of PRA above the adult range were frequently observed in children (Fig 1). In the 108 children and adults (age range, 4 to 76 years), PRA was negatively correlated with age (r = -.49; P < .0001).

Active Renin

The mean concentration of active renin in plasma was highest in infants and decreased with increasing age in each group of children, with the lowest concentration being observed in adults (Table). Over the age range of 4 to 76 years, active renin concentration was negatively correlated with age (r = -.47; P < .0001) (Fig 2).

Prorenin (Inactive Renin)

Mean plasma prorenin concentration was significantly lower in children and adolescents than in adults, resulting in a positive correlation of plasma prorenin concentration with age (r=.48; P<.0001), but the range of plasma prorenin concentrations in each group was quite similar (Fig 3). In infants, however, plasma prorenin concentrations were higher than those found in children and adolescents. As expected, prorenin concentration was significantly correlated with active

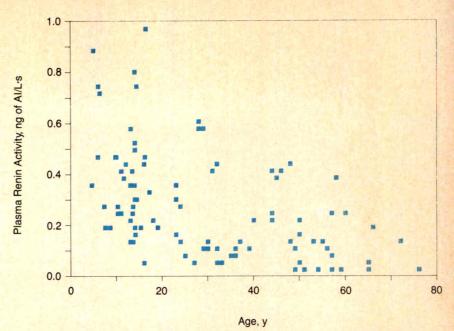


Fig 1.—Plasma renin activity among children and adults. Al indicates angiotensin I.

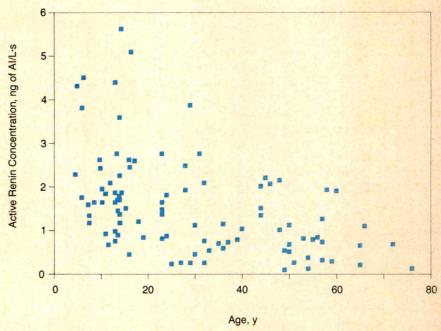


Fig 2.—Active renin concentration among children and adults. Al indicates angiotensin I.

renin concentration among the children, adolescents, and adults (r = .92; P < .0001).

COMMENT

There is general agreement that PRA and the active renin concentration in children and adolescents are the same or higher than among older adults. 7-11 Fiselier et al 10 found very high concentrations of plasma prorenin in infants, while children 1 to 16 years of age had concentrations of prorenin within the normal adult range. On the other hand, Blazy et al 11 found prorenin concentrations too low

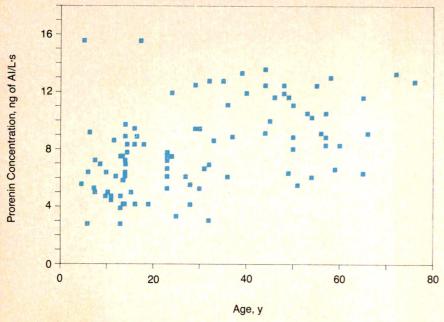


Fig 3.—Prorenin concentration among children and adults. Al indicates angiotensin I.

to measure in infants, while in children 1 to 15 years old, prorenin concentrations were slightly higher than in normal adults. In our group of 50 children and adolescents, plasma prorenin concentrations varied over a wide range and were slightly lower than those found in adults, resulting in a positive correlation with age over the range of 4 to 76 years.

Plasma prorenin concentrations were higher in umbilical cord blood samples obtained from newborns than in the peripheral blood samples obtained from older children or adults, a finding in agreement with those of Fiselier et al¹⁰ and Siegel et al.¹² It is likely that methodologic differences account for the diverse results that have been reported in the past.

In previous studies, PRA and pro-

renin in plasma of children have been compared with similar measurements in adults of unspecified ages.8,10 When the ages of normal adults are taken into account, there is a significant decline in PRA and active renin concentration from infancy to old age. The relation of plasma prorenin concentration to age is more complex, as very high prorenin concentrations occur in infants, followed by a decline to lower concentrations in adolescents, and then a small increase with age in adulthood.

There is substantial data suggesting that elevated plasma prorenin concentrations are associated with microvascular complications and autonomic neuropathy in adults with diabetes. The age-related normal values for prorenin presented in this study will facilitate investigations to determine if elevated prorenin concentrations predict the development of complications in children and adolescents with dia-

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In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY-HEAD & NECK SURGERY Effects of Cleft Lip and Palate on the Nasal Airway in Children

Donald W. Warren, DDS, PhD; W. Michael Hairfield, DDS, MS; Eileen T. Dalston, MA; James D. Sidman, MD; Harold C. Pillsbury, MD (Arch Otolaryngol Head Neck Surg 1988;114:987-992)

Occult Bacteremia in Children With Simple Febrile Seizures

James M. Chamberlain, MD, Richard L. Gorman, MD

• The controversy surrounding the diagnostic workup for simple febrile seizures has centered around the lumbar puncture. This focus has obscured the potential importance of other tests. A retrospective study was performed to determine the frequency of occult bacteremia in simple febrile seizures. In a pediatric emergency department, we identified 115 cases of simple febrile seizures in children treated as outpatients. Blood cultures were performed in 93 (81%) of 115 patients; five (5.4%) were positive. Children were less likely to have blood cultures performed if they were older than 24 months or had a medical history of simple febrile seizures. However, neither age nor history of febrile seizures affected the risk of bacteremia. These data suggest that patients with simple febrile seizures are at approximately the same risk for bacteremia as children with fever alone. Patients with simple febrile seizures should be treated in the same manner as other patients of the same age with regard to the performance of blood cultures.

(AJDC 1988;142:1073-1076)

Seizures associated with fever are a common pediatric problem. It is estimated that 3% to 5% of the population will experience a simple febrile seizure. The controversy surrounding the diagnostic workup for a seizure and fever has centered around the lumbar puncture because of the importance of excluding bacterial meningitis. This focus has obscured the

potential importance of other diagnostic tests.

To our knowledge, the use of blood cultures in the diagnostic workup of this subset of febrile patients has never been systematically evaluated. Specifically, there has been no study examining the frequency of occult bacteremia in patients with simple febrile seizures despite several studies in children with fever alone. A retrospective study was performed to assess the occurrence of occult bacteremia in children with simple febrile seizures who were treated as outpatients.

PATIENTS AND METHODS

The study was performed at the University of Maryland Hospital Pediatric Emergency Department (PED), Baltimore. The PED serves an inner-city population from birth to 18 years of age. There are approximately 20 000 visits yearly to the PED.

Data were collected for 41 months using the following methods. From June 1, 1983 to Oct 31, 1984, the emergency room intake log was inspected to identify chief complaints suggestive of seizures. Charts with chief complaints such as fainting, shaking, seizures, convulsions, fits, "fell out," "out of it," and the like were retrieved from medical records to determine if the patient had had a seizure associated with fever. From Nov 1, 1985 to Oct 31, 1987, the charts of all patients seen in the PED were reviewed daily to identify episodes of seizures with fever. The pediatric residents were reminded periodically that all patients with seizures and fever should have blood cultures performed.

Children with seizure and fever had their ambulatory record abstracted onto a standard data collection instrument. Data collected included age, date of visit, description of the seizure type and duration, vital signs, laboratory evaluations, medications, medical history, diagnosis other than seizure, and disposition.

After identifying all episodes of seizures with fever, the data were further analyzed

to identify simple febrile seizures in children who were treated as outpatients. Specific inclusion criteria were as follows: (1) seizure with rectal temperature greater than 38°C; (2) age between 1 month and 7 years; (3) not admitted to the hospital; (4) no prior neurologic disease; (5) no immunization within 72 hours of the seizure; and (6) simple febrile seizure as defined below.

A simple febrile seizure is a generalized tonic-clonic seizure lasting less than 15 minutes, with no more than one seizure occurring in a 24-hour period, and not associated with recognized neurologic or systemic disease such as meningitis or dehydration. In contrast, a complex febrile seizure is focal in nature, prolonged in duration, or occurs more than once a day. Patients with complex seizures were excluded.

For the purposes of this study, preexisting neurologic disease included afebrile seizures, cerebral palsy, hydrocephalus, or developmental delay. Such patients were excluded from analysis. Patients who were admitted to the hospital were excluded because they had meningitis or "looked ill" and therefore could not have occult bacteremia.

The standard procedure for obtaining blood cultures in the emergency department follows. Blood specimens are drawn from an aseptically prepared peripheral site and at least 0.5 mL is inoculated into tryptic soy broth using aerobic and anaerobic media (BACTEC, Johnston Laboratories, Towson, Md). Activity of metabolized radioactive carbon is measured every 12 hours. Cultures are positive when identification of a pathogenic organism is made. Cultures are negative if no such determination can be made in seven days. If a blood culture was positive, follow-up was arranged and patient outcome was determined. Data were analyzed using summary statistics, the χ^2 test, and Fisher's exact

RESULTS

During the study period, there were 195 identified episodes of seizures associated with fever. Patients ranged in

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| Cultured | 62 | 31 |
|--------------|--------------|--------|
| | 5-24 mo | >24 mo |
| Cultures as | a Function o | n Age |
| Table 1.—The | | |
| | | |

15*

| *v2 | | |
|-----|--|--|
| | | |

Not cultured

| ory |
|-----|
| |

 $^{*\}chi^2 = 14.91$.

age from 5 months to 6 years. From these 195 episodes, 42 patients were admitted to the hospital and therefore excluded from analysis. Of the remaining 153 children treated as outpatients, 38 patients were excluded. These patients were excluded for the following reasons: 23 children had prior neurologic disease, two had recent immunizations, and 13 had complex seizures. The episodes of 115 remaining children with simple febrile seizures who were treated as outpatients were analyzed.

Of the 115 episodes of simple febrile seizures in children treated as outpatients, 69 seizures occurred in children less than 2 years of age and 46 seizures occurred in children 2 years of age or older. In 62 (90%) of 69 children less than 2 years old, blood cultures were obtained, whereas in patients 2 years of age or older, 31 (67%) of 46 children had blood cultures performed $(\chi^2 = 9.00, P < .01, Table 1)$. Patients without a history of febrile seizures more frequently had blood cultures performed than those with a history $(63/68 \text{ vs } 30/47, \chi^2 = 14.91, P < .001,$ Table 2).

Of the 115 cases suitable for analysis, 93 patients had blood cultures performed, of which five (5.4%) were positive. All cultures were positive for Streptococcus pneumoniae. There were three (4.8%) of 62 positive cultures in the less-than-2-years-of-age group and two (6.4%) of 31 in the 2-years-and-older group. The five bacteremic patients consisted of four girls and one boy ranging in age from 15 to

Table 3.—Sensitivity, Specificity, and Predictive Values of Age, Fever, and Leukocyte Count for Bacteremia*

| | Blood Cul | ture Result | |
|---|-----------|-------------|--|
| | Positive | Negative | Determinants of Validity |
| Age, y | | | |
| ≤2 | 3 | 59 | Sensitivity 60%, |
| >2 | 2 | 29 | specificity 33%, PPV 4.8%, NPV 93.5% |
| Fever, °C | | | |
| ≥39 | 5 | 79 | Sensitivity 100%, |
| <39 | 0 | 9 | specificity 10.2%, PPV 6.0%, NPV 100% |
| WBC, ×10°/L | | | |
| ≥15 | 4 | 20 | Sensitivity 80%, |
| <15 | 1 | 67† | specificity 77%, PPV 16.7%, NPV 98.5% |
| Combination of age <2 y, temperature >39°C, and WBC >15 × 10°/L | 2 | 10 | Sensitivity 40%, specificity 88.5%, PPV 16.7%, NPV 96.39 |
| Absence of the combination | 3 | 77† | |

^{*}PPV indicates positive predictive value, and NPV, negative predictive value. †One patient had a blood culture but no leukocyte count.

30 months. Two of the five patients with positive blood cultures had a medical history of simple febrile seizures. There was no significant difference in the occurrence of positive blood cultures in those with and without a history of febrile convulsions (2/30 vs 3/63 positive, P=1.0, two-tailed Fisher's exact test). The rate of performance of blood cultures was similar during the first and second study periods (77% and 82.5%, respectively), despite frequent reminders to the house staff during the second study period.

Of those patients with a positive blood culture, the mean leukocyte count was $20.9 \times 10^9/L$ and the mean temperature was $40.2^{\circ}C$. Of those patients with negative blood cultures, the mean leukocyte count was $13.1 \times 10^9/L$ and mean temperature was $39.8^{\circ}C$. Neither of these differences achieved statistical significance. Fourteen patients with negative blood cultures had white blood cell counts greater than $15 \times 10^9/L$, but no bacteremic patient had a white blood cell count less than $14.8 \times 10^9/L$.

The sensitivity, specificity, and predictive values of age less than 2 years, fever greater than 39°C, and leukocyte count greater than $15 \times 10^9/L$ for bacteremia are depicted in Table 3. The leukocyte count was the most valuable of the three for predicting the presence of bacteremia. Both temperature

less than 39° C and leukocyte count less than $15 \times 10^{\circ}$ /L were predictive of a negative blood culture in our study population. The combination of the three variables provided a sensitivity of 40%, a specificity of 88.5%, a positive predictive value of 16.7%, and a negative predictive value of 96.3%.

Follow-up of patients with a positive blood culture included a telephone call and a return visit to the PED. Blood cultures were then repeated. All repeated cultures were negative and all patients recovered without complication. Three of the five children had been treated with amoxicillin suspension for otitis media; two carried only the diagnosis of "simple febrile seizure" and had not been treated with antibiotics.

There were 42 patients admitted to the hospital for febrile convulsions. Eighteen patients were admitted for complex seizures, nine of whom presented in status epilepticus. There were nine with meningitis, three with pneumonia, and eight with otitis media. There were also patients with mastoiditis, facial cellulitis, and reactions to the diphtheria, pertussis, and tetanus vaccine. There were only three patients admitted to the hospital with the sole diagnosis of simple febrile seizure; one had a positive blood culture for *S pneumoniae*.

COMMENT

To our knowledge, the value of blood cultures in the diagnostic workup of

children with simple febrile seizures has not been previously evaluated in the medical literature. Gerber and Berliner² reviewed routine diagnostic tests performed on 100 consecutive patients admitted to the hospital with their first febrile seizure. They studied nine separate tests, including lumbar puncture, electroencephalogram (EEG), and skull roentgenogram, but they made no mention of blood cultures. Of the nine tests studied, only the complete blood cell count provided significant positive information regarding the presence of disease. Asnes et al³ performed a nationwide survey of 266 pediatricians to determine their routine workup. Blood cultures were not discussed. In a more recent survey, Chessare and Berwick⁴ polled 336 Boston physicians regarding workup of their patients. Admission to the hospital, lumbar puncture. performance of an EEG, and referral to a neurologist were discussed; blood cultures were not. Vining and Freeman⁵ stated that "the workup of a child who has had a febrile seizure and has recovered, consists solely of the workup of the fever," but they did not specifically address the utility of blood cultures. In a review of 39 children admitted to the hospital with a first febrile seizure, Surpure6 reported that 31 blood cultures were performed but no mention was made of routine blood cultures. The American Academy of Pediatrics Consensus Statement from 1980 covers briefly the initial workup for febrile seizures: blood cultures were not included in their recommendation.7

Despite the publication of several articles from 1973 to 1978 addressing the issue of occult bacteremia in febrile children, 8-12 it has been only recently that bacteremia has become a serious consideration in patients suffering from febrile convulsions. Hamrick and Murphy,11 in a study of 28 bacteremic outpatients, noted that five (18%) of 28 patients with bacteremia had presented with a febrile seizure. It is not clear from their data whether these children had meningitis or were in the group that recovered without sequelae. In a study by McIntyre et al. 13 ten of 15 retrospectively identified patients with occult pneumococcal bacteremia had presented with seizures and fever. However, the overall occurrence of bacteremia in patients admitted to the hospital with febrile convulsions was 2.3%. Lewis et al, in studying the role of viruses in the pathogenesis of febrile convulsions, incidentally reported that one of 73 blood cultures was positive. This patient had meningitis and would have been excluded from the present data set.

The studies of McIntyre et al¹³ and Lewis et al¹⁴ suggest that the frequency of bacteremia in children with febrile seizures is only 1% to 2%. This finding differs from the results of several studies concerning occult bacteremia with fever.⁸⁻¹² These studies found rates of 3.2% to 7.3% in patients less than 2 years of age with fever alone.

These data represent the first determination of the risk of occult bacteremia in children with simple febrile seizures treated as outpatients. There were 93 identified episodes of simple febrile seizures in which blood cultures were performed. Of the 93 cultures, five (5.4%) were positive. There were 22 outpatients with simple febrile seizures in whom blood cultures were not performed. If cultures had been performed in all of the 115 outpatients with simple febrile seizures and the additional 22 were negative, the positive rate would have been 4.3% (5/115)

The data presented in this study suggest that children with simple febrile seizures are at approximately the same risk for bacteremia as other children with fever alone. The overall positive rate of 5.4% of performed blood cultures is in the published range of 3.2% to 7.3% for children with fever alone seen in comparable clinical situations. 8-12

The 5.4% frequency of bacteremia in this sample of patients with simple febrile seizures suggests that blood cultures are a useful diagnostic aid for outpatient evaluation. Previous studies have shown that other tests, including lumbar puncture, serum chemistry studies, EEG, have not yielded such a high rate of positive results. 2.6.16-17

High fever, high leukocyte count,

and young age have previously been identified as risk factors for bacteremia. $^{8\cdot10,12}$ In this study, all patients with bacteremia had temperatures of 39.4°C or greater and leukocyte counts greater than 14.8×10^{9} /L. All bacteremic patients were less than 3 years of age.

Physicians are less likely to perform blood cultures in a patient with a medical history of febrile seizures (Table 2). It is important to note, however, that two of five patients with bacteremia in our study had a history of febrile seizures. One of these patients was bacteremic during her third episode. A history of febrile seizures should not dissuade the emergency room physician from performing blood cultures.

There are several limitations to this study. Despite a relatively long study period and the identification of 195 episodes of seizures associated with fever, only 93 cases were identified that met our criteria of patients with simple febrile seizures, discharged from the emergency department, who had blood cultures performed. There were only five positive blood cultures. and it is difficult to compare this result directly with previously published reports concerning bacteremia in children with fever. Despite the limitation of small numbers of positive cultures, we have demonstrated that bacteremia does occur in children with simple febrile seizures. The frequency of positive blood cultures is within the published range of 3.2% to 7.3% for children with fever alone. A prospective study with a control group of febrile children would be necessary to directly compare the risk of occult bacteremia in the two groups.

The study was performed in a large inner-city hospital under clinical conditions similar to several previous studies of occult bacteremia. Caution should be applied in generalizing these results to other populations. The data were collected retrospectively and therefore may have been subject to biases, such as the previously discussed bias against performing cultures in those patients with a history of febrile seizures. Only episodes of simple febrile seizures in which the children were treated as outpatients

were included, but a selection bias to perform blood cultures in the more seriously ill-appearing patients cannot be completely excluded. However, in 90% of patients less than 2 years old and in 81% of all children, blood cultures were performed. There is a small possibility that a few patients with simple febrile seizures may have had subsequent convulsions, making them, in fact, complex seizures. Parents were instructed to return if seizures recurred and none did so within 24 hours except as excluded above.

CONCLUSIONS

The data suggest that patients with simple febrile seizures are at approximately the same risk for occult bacteremia as patients with fever alone. These patients should receive the same consideration with respect to more recent controversy concerning expectant treatment with antibiotics for those patients at high risk for bacteremia. 18-20 Patients with simple febrile seizures should be treated in the same manner as other patients of

the same age when performing blood cultures.

Carol Carraccio and Margaret Rennels gave editorial assistance, and Patricia Schmidt assisted with the manuscript.

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Animals in Research and Testing: Who Pays the Price for Medical Progress? Steven J. Smith, PhD; Jerod M. Loeb, PhD; R. Mark Evans, PhD; William R. Hendee, PhD (Arch Ophthalmol 1988;106:1184-1187)

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Special Features

Radiological Case of the Month

Robert G. Wells, MD, John R. Sty, MD (Contributors); Lionel W. Young, MD (Editor for This Case); Beverly P. Wood, MD (Section Editor)

Accepted and edited for publication by Lionel W. Young, former section editor, May 11, 1987.
From the Department of Radiology, Children's Hospital of Wisconsin, Madison.

Reprint requests to Department of Radiology, Children's Hospital Medical Center of Akron, 281 Locust St, Akron, OH 44308 (Dr L. W. Young).

A 2-year-old boy was examined for increasing head size after a fall that had occurred one month earlier. No associated neurologic findings were detected. The anterior fontanelle was open but tense. The optic fundi

showed no papilledema. Results of routine blood and urine laboratory examinations were normal. A computed tomographic examination of the head was part of the investigation of the etiology of macrocrania (Figs 1 to 3).

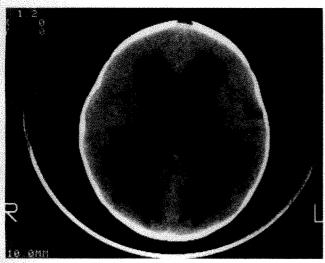


Figure 1.

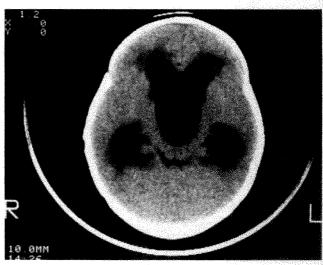
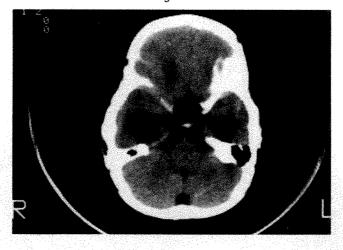


Figure 2.





Denouement and Discussion

Suprasellar Arachnoid Cyst

Fig 1.—Cranial computed tomogram of head shows markedly dilated lateral ventricles.

Fig 2.—Computed tomogram of head at lower axial level shows dilated temporal horns and large cystic structure in region of third ventricle.

Fig 3.—Computed tomogram of head 1 cm lower than axial level in Fig 2 shows posterior extension of suprasellar cystic structure and posterior displacement of basilar artery and brain stem.

Congenital arachnoid cysts may occur in a variety of intracranial sites, but a suprasellar location is rare. Nearly 70 published cases of suprasellar arachnoid cysts were found in a literature review.¹³

Seventy-five percent to 90% of patients with congenital subarachnoid cysts present with hydrocephalus in infancy or early childhood.¹ Older patients may present with headaches and hypopituitarism. Associated macrocrania is present in approximately 50% of patients,¹ while impaired visual acuity and/or abnormal visual fields are found in 25%.¹ To-and-fro bobbing and nodding of the head and trunk ("bobble-head doll syndrome") and isosexual precocious puberty may occur.⁴ An ataxic gait may be detected in about 25% of older children.

Starkman et al⁵ proposed the now commonly accepted theory of the etiology of arachnoid cysts. They found that the walls of arachnoid cysts consist of membranes that are contiguous at the cyst margins with normal arachnoid tissue. The arachnoid cyst does not lie within the true subarachnoid space but rather between two layers of arachnoid tissue; therefore, the cyst should properly be termed intraarachnoid cust. The cyst may enlarge with time as the result of a ball-valve action at the point(s) of communication between the cyst and the subarachnoid space.

Computed tomography and/or ultrasonography performed for suspected hydrocephalus characteristically demonstrate enlargement of the lateral ventricles and a cystic structure in the region of the anterior aspect of the third ventricle.² The fourth ventricle typically is normal. A major diagnostic pitfall is mistaking the cyst for a dilated third ventricle and concluding that aqueductal stenosis is present. Usually, disproportionate enlargement of the cyst in the region of the anterior portion of the third ventricle can be appreciated. The cyst wall is sometimes imaged, thus separating the cyst from the dilated third ventricle.

The best method of investigating patients with suspected subarachnoid cysts is computed tomographic metrizamide ventriculography.6 A small volume of metrizamide contrast medium is instilled via a diversionary shunt catheter into the lateral ventricle. Computed tomography is delayed until two to four hours after the injection to allow diffusion of metrizamide throughout the ventricular system. Typically, the enlarged lateral ventricles are well opacified with the contrast material. The cyst does not readily communicate with the ventricular system and retains the low attenuation characteristics of cerebrospinal fluid. The third ventricle is usually opacified and is typically displaced superiorly and posteriorly by the cyst.

Differentiation between hvdrocephalus secondary to congenital aqueductal stenosis and hydrocephalus due to a suprasellar arachnoid cyst is essential for proper treatment. Rouventriculoperitoneal shunting may decompress one ventricle, and dilatation of both the cyst and the unshunted lateral ventricle may persist. A transcallosal approach may be used to decompress the cyst by establishing communication between the suprasellar cyst and the ventricular system.1 This was the method of treatment in the present patient. In patients with hydrocephalus and visual impairment, a subfrontal approach may be used to establish communication between the cyst and the basal cisterns. With obliteration of the cyst via decompression, many patients eventually become shunt independent.

This patient has had no recurrent hydrocephalus and is doing well two years after diagnosis and treatment. His growth and development have been normal.

The increasing use of high-resolution computed tomography for the investigation of childhood hydrocephalus may lead to a greater frequency of detection of suprasellar arachnoid cysts. Specific inspection of the third ventricle and suprasellar region is essential in all cases of suspected congenital aqueductal stenosis to exclude obstruction secondary to a cyst. Current improved methods of investigation and treatment are encouraging that most of these children may achieve normal growth and neurologic function.

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Picture of the Month

Raanan Arens, MD (Contributor); Murray Feingold, MD (Section Editor)



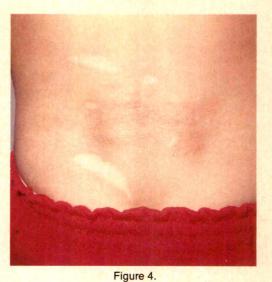
Figure 1.



Figure 2.



Figure 3.



Accepted for publication Jan 3, 1988.
Contributed from The Chaim Sheba Medical
Center, Tel-Hashomer, Israel.
Reprint requests to National Birth Defects
Center, Kennedy Memorial Hospital, 30 Warren
St, Boston, MA 02135 (Dr Feingold).

Denouement and Discussion

Fig 1.—Shagreen patch.

Fig 2.—Adenoma sebaceum.

Figs 3 and 4.—Hypopigmented macules.

Manifestations

Tuberous sclerosis is a major genetic cause of mental retardation and intractable seizures. A variety of lesions are present in multiple organs, including the brain, skin, eyes, kidneys, heart, bones, and lungs. These lesions consist of cells of more than one type, eg, fibroblasts, angioblasts or glioblasts, and neuroblasts. Convulsions are the most common clinical sign of brain involvement and occur in more than 90% of patients. Mental retardation, varying from mild to severe, is present in 60% to 70% of patients. The characteristic cerebral lesions are sclerotic patches (tubers) scattered throughout the cortical gray matter. There may also be multiple small tumor nodules with a periventricular distribution. These tumors usually enlarge, become calcified, are frequently present in the basal ganglion, and may undergo malignant transformation.

Skin manifestations present during

infancy or later in childhood include hypopigmented macules in approximately 85% of patients. These lesions are hypomelanotic macules, usually located on the trunk or limbs, and have a round, oval, or ash-leaf shape. Adenoma sebaceum forms well-developed facial lesions that are pathognomonic of tuberous sclerosis and are present in 90% of patients over 4 years of age. These tumorlike lesions are angiofibromas. A characteristic skin lesion is the shagreen patch. It generally appears as a flat or slightly elevated area and is red or flesh colored with a "pigskin" or "orange peel" appearance. Nails are another common site of fibromatous involvement and in some patients subungual fibromas disrupt the entire nailbed.

Gray-yellow plaques in the retina near the optic disc (phakomas) are present in approximately 50% of patients. Teeth may have pitlike enamel defects. Other benign tumors consisting of a mixture of fibrous tissue, fat,

blood vessels, and smooth muscle are found in numerous organs, especially the kidneys, heart, lungs, and bones.

Genetics

Tuberous sclerosis has an autosomal dominant inheritance with a wide variation of expression. Approximately 50% of the patients appear as a new mutation.

Treatment

No specific treatment is available. Seizures are managed with anticonvulsant medications. Surgical excision of the tumors is indicated only if they are symptomatic. Genetic counseling should be provided.

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The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

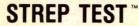
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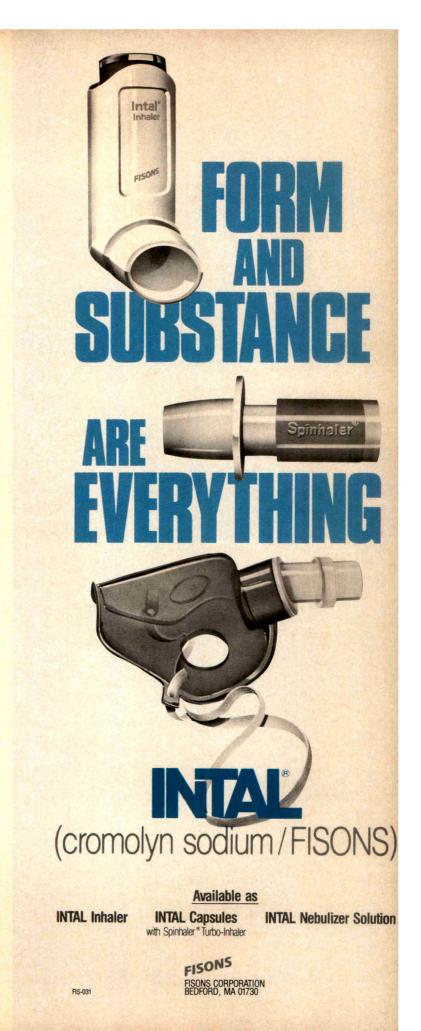
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Outcome of Neonatal Strokes

Sarbjeet K. Sran, MD, Robert J. Baumann, MD

· We examined the clinical outcome of 17 children, 1 to 11 years of age, who experienced major cerebral artery infarctions (strokes) as neonates. Nine of the 17 children had left middle cerebral artery (MCA) infarctions, five had right MCA infarctions, two had bilateral MCA infarctions, and one had a left posterior cerebral artery infarction. Fourteen of the 17 children developed seizures as neonates. Most of these children who developed seizures were neurologically abnormal as neonates, became seizure free and neurologically normal early in the first year of life, and their anticonvulsant therapies were discontinued. After a seizure-free period of one to eight years, three of the 14 patients again required anticonvulsant therapy for seizure control. Two of the 16 surviving children continue to be severely handicapped while 11 of the 16 are making apparently normal developmental progress. One of the two children presently attending school has cognitive deficits appropriate to the site affected by the original infarction. Most children with neonatally diagnosed strokes appear to have a good short-term outcome, but later onset of seizures and subsequent recognition of cognitive deficits may not be uncommon.

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Since 1979 when Barmada and coworkers1 noted a 5.4% incidence of cerebral infarction in neonatal autopsies, the occurrence of major neonatal cerebral artery infarctions has been increasingly recognized.2-10 Most reports emphasize the diagnosis and short-term outcome of neonatal infarction.8-7 However, we are aware of only one long-term follow-up study comprising ten infants.2 Since the outlook for these infants remains unclear, we traced the outcomes of 17 such children, 1 to 11 years of age, for an average follow-up period age of 3 years 2 months.

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PATIENTS AND METHODS

We reviewed the medical records of all neonates born in or admitted to the University of Kentucky Hospital, Lexington, between January 1975 and January 1986 with the diagnosis of cerebrovascular accident or seizure. We also reviewed all computed tomographic (CT) reports to identify neonates with imaged arterial distribution infarctions. Preset criteria for inclusion in the study were a roentgenographically imaged arterial brain infarction within the first 30 days after birth or clinical evidence of a focal abnormality of the brain in the neonatal period confirmed by subsequent roentgenographic imaging consistent with an arterial infarction. Selected perinatal and follow-up data were obtained from medical record review. Most patients were examined by a neurologist at our institution one year or less before the completion of this study on Nov 1, 1987. For the two patients no longer being cared for at our institution, specific information about medical history and physical examination was obtained by telephone from their pediatricians. Most parents were contacted by telephone for additional follow-up information concerning common developmental achievements (age at sitting, walking, and talking); hand preference for eating and writing; asymmetrical strength or smile; school performance; and history of seizures and anticonvulsant usage. With parental permission, we obtained school records for the two school-age children.

RESULTS

Seventeen children, aged 1 to 11 years, met our preset study criteria (Tables 1 and 2). A review of the perinatal data showed that all but one infant were born of term gestations. Major neonatal complications affected five infants. The complications included congenital nephrosis (patient 6), protein C deficiency (patient 7), congenital thrombocytopenia (patient 10), premature twin gestation (patient 9), and severe dehydration with hyponatremia from gastroenteritis (patient 12). Seven additional infants had other perinatal risk factors; meconium staining at delivery and Apgar score of less than 7 at five minutes (patients 1 and 7); meconium staining at delivery (patients 1, 4, and 8); nuchal cord

(patients 15 and 16); and midwife delivery with no clinical record available (patient 11). The other infants were products of unremarkable vaginal deliveries.

Fourteen of the 17 infants presented with seizures (12 with focal seizures) during the neonatal period. One child presented with a persistent unilateral gaze. For 15 subjects the cerebral artery infarction was identified by CT scan (14 patients) or nuclide scan of the brain (one patient) during the neonatal period. One infant with a right focal seizure and left-sided sharp waves on electroencephalogram had a left middle cerebral artery (MCA) infarction on his first CT done at 9 years of age. The infant with persistent left lateral gaze had a left MCA infarction when the first image was done at 6 months of age. Nine (53%) of the 17 lesions involved only the left MCA while five (29%) involved only the right MCA. Two additional children (12%) had bilateral MCA lesions, and one (6%) had a posterior cerebral artery lesion.

The average age at follow-up was 3 years 2 months with a range from 1 year to 11 years. One child (patient 6) died of congenital nephrosis and is not included in the follow-up data. Eleven of the 16 surviving children had apparently normal development; three children showed mild developmental delay; and only two children, both with bihemispheric lesions, manifested severe developmental delay. Three of the ten children with left hemispheric lesions had a mild hemiparesis while one child had a moderate hemiparesis. Two additional children with left hemispheric injuries were left-handed without any strong family history of the same. In the five children with right hemispheric lesions, no hemiparesis was noted, but two children were described as "clumsy" by their parents. Thirteen children appeared to have normal vision and one child had a right hemianopia; however, both children with bilateral lesions were blind. After an initial period of seizure activ-

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Table 1.—Perinatal Data for 17 Children With Neonatally Diagnosed Stroke* Age, Type of Age at Brain Imaging, Age. EEG Birth Apgar Score. First Findings **Patient** Weight, g History **Symptom** Symptom Finding 1 min/5 min 44 wk; meconium; C-sec; 9 y, CT, L MCA 3320 NA **Birth** R focal 1 d, L sharp wave maternal infection seizure 2 4 d. BS. R MCA 6 d. R side spikes 4270 7/9 Term: benian 4 d L focal seizure 3 2730 7/8 Term; forceps delivery 3 d R focal 13 d, CT, L PCA 5 d, L side seizure suppression 3415 6/7 Term: meconium 1 d L focal 6 d, CT, R MCA 3 d. R occipital seizure sharp waves 3 d, R temporal 5 3240 8/9 Term; benign 5 h Apnea 3 d, CT, R MCA focus 6 2720 3/7 38 wk: C-sec: congenital 12 h Generalized 1 d. CT. L MCA and 1 d. diffusely nephrosis seizures R MCA abnormal 1 d, CT, L MCA and 2860 8/9 Term; C-sec; protein C 2 d Generalized 7 d, diffusely deficiency seizures porencephalic cyst abnormal R 2980 8/9 Term; C-sec; meconium R focal 1 d, CT, L MCA 1 d, L frontal 1 d seizures spikes 1420 5/7 30 wk; twin None 4 d, CT, R MCA and 3 d, normal L MCA 10 3880 7/8 42 wk; thrombocytopenia 6 d R focal 6 d, CT, L MCA 10 d, L frontal seizures spikes 11 5020 NA Term; benign Left lateral 5 mo, CT, L MCA 5 mo, multifocal 2 wk spikes gaze 12 2880 9/9 Term; severe dehydration L focal 3 wk, CT, R MCA 3 wk, R side 3 wk at 3 wk seizures spikes 13 4200 8/9 Term; benign 3 d L focal 3 d, CT, L MCA 4 d, L side sharp seizures waves 14 2700 8/9 Term; benign 1 d, CT, L MCA 1 d R focal 3 d, bihemispheric seizures sharp waves R focal 15 3570 NA Term: nuchal cord 3 d, CT, L MCA 3 d seizures 16 5100 8/9 43 wk; nuchal cord R focal 2 d, CT, L MCA 2 d, diffusely 2 d seizures abnormal 17 3000 1/4/7† 42 wk; C-sec; meconium L focal 1 d, CT, R MCA and 1 d, R side spikes seizures **RIVH**

*NA indicates not available; C-sec, cesarean section; CT, computed tomogram; BS, brain scan; MCA, middle cerebral artery; PCA, posterior cerebral artery; IVH, intraventricular hemorrhage; and EEG, electroencephalogram.

†Apgar scores taken at 1, 5, and 10 minutes after birth.

ity early in neonatal life, all children (14 patients) became free from seizures while receiving phenobarbital. Of the 14 children for whom phenobarbital therapy was discontinued at 6 months to 2 years of age, three have developed seizures and require administration of anticonvulsant medication. These three children had been free of seizures and had received no anticonvulsant medication for one to eight years.

Two of the 16 children are presently in school. One child, who has a right hemispheric lesion, is doing well in all school subjects; however, the other child, who has a left hemispheric lesion, showed the following scaled scores on the Weschler Intelligence Scale for Children: Arithmetic, 8; Similarities, 9; Vocabulary, 6; Comprehension, 3; and Full-Scale IQ, 76.

COMMENT

Since the autopsy study by Barmada et al¹ in 1979, there has been increasing recognition of the link between neonatal arterial infarction (stroke) and neurologic disabilities in later childhood.2-13 Nevertheless, many questions about neonatal stroke remain unresolved. What is the incidence of neonatal stroke? Incidence data are unavailable in part because it is difficult to design a study to identify all the infants in whom cerebral infarction has occurred. In other studies like ours, neurologic diagnostic testing is obtained only for neonates who exhibit neurologic symptoms. Though identifying infarction in neurologically symptomatic neonates and obtaining autopsies of neonatal deaths will detect many (perhaps most) neonatal infarctions, there are asymptomatic

cases that will be missed. In our earlier studys we found that over one third of the children with roentgenographic evidence of previous arterial infarction had no history of having had a neonatal seizure or other adverse event. These children had an apparently uneventful neonatal course. The subset of children with neonatal stroke who are asymptomatic in the neonatal period are likely to have different outcomes from the children whose cases are reported in this study, 16 of whom were symptomatic shortly after birth.

In the short term, the children with symptomatic neonatal infarctions did surprisingly well despite often having large cystic-appearing lesions on CT scan. Many of these lesions seemed to encompass most or all of the territory of the MCA. However, most of the children made good developmental

| Patient | Lesion | Age | Developmental Status | Handedness | Neurologic Status | Seizures/ Anticonvulsants |
|---------|-----------------------|-------------|-------------------------------------|-----------------|--|------------------------------|
| 1 | LMCA | 11 y | Mild delay | R | Mild R hemiparesis | Controlled/ phenobarbital |
| 2 | R MCA | 8 y | Normal | R | Normal | None/none |
| 3 | L PCA | 5 y 6 mo | Normal | R | Normal | None/none |
| 4 | R MCA | 4 y | Mild delay | R | "Clumsy" | Controlled/ phenobarbital |
| 5 | R MCA | 3 y | Normal | L (positive FH) | "Falls a lot" | None/none |
| 6 | L MCA and R MCA | Died at 1 y | ••• | *** | ••• | |
| 7 | L MCA | 2 y 8 mo | Sits up; speaks words; severe delay | • • • | Blind; abnormal | None/none |
| 8 | L MCA | 2 y 6 mo | Normal | L | Mild R hemiparesis | None/none |
| 9 | L MCA and R MCA | 2 y 6 mo | Severe delay | R | Hydrocephalus, brisk reflexes | None/none |
| 10 | L MCA | 2 y 6 mo | Normal | L (positive FH) | Normal | None/none |
| 11 | L MCA | 1 y 9 mo | Mild delay | L | R Hemianopia; moderate R hemiparesis | None/none |
| 12 | R MCA | 1 y 10 mo | Normal | R | Normal | Controlled/ phenobarbital |
| 13 | L MCA | 1 y 7 mo | Normal | Both | Normal | None/none |
| 14 | L MCA | 1 y | Normal | * * * | Normal | None/none |
| 15 | L MCA | 1 y 1 mo | Normal | Both | Minimal R hemiparesis | None/none |
| 16 | L MCA | 1 y | Normal | R | Mild bilateral crossed adductors | None/none |
| 17 | R MCA and R IVH | 1 y | Normal | R | Normal | None/none |

^{*}MCA indicates middle cerebral artery; PCA, posterior cerebral artery; IVH, intraventricular hemorrhage; and FH, family history.

progress with relatively mild motor signs. They also had minimal morbidity from their seizures. All 14 children with neonatal seizures were free of seizures while receiving phenobarbital. As they grew older, the phenobarbital dose was successfully diminished and discontinued. Nevertheless, three of the children subsequently had recurrence of their seizures. It does not appear that the underlying arterial infarction made their seizures as neonates more persistent or more difficult to control.

The etiology of neonatal arterial infarctions remains unclear. As pointed out by Barmada et al,¹ some of the infarctions have actually occurred in utero, days or weeks before delivery. Ment and colleagues³ have appropriately emphasized the probable causal role of bradycardia and hypotension in infants who have suffered asphyxia. Additionally, thrombosis (as in patient 7) and embolism are likely mechanisms in some patients.⁵ In both this and our previous

study,⁸ no clear causal mechanism could be postulated for most of the instances of neonatal arterial infarction

Our data suggest that pediatricians can tell families that, in the short term, infants discovered to have had a single, unilateral arterial stroke do well. Their seizures are generally easy to control and most of the children make good developmental progress. Nevertheless, these children require careful long-term supervision since their seizures may recur. Moreover, an unknown number of these youngsters will eventually demonstrate cognitive handicaps and require special educational assistance.

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Bloom's Syndrome

Clinical Features and Immunologic Abnormalities of Four Patients

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 Immune function was studied in four patients (two girls and two boys, aged 30 months to 24 years) with documented Bloom's syndrome. Three patients had a decreased serum concentration of at least one subclass of immunoglobulins. All had normal or elevated proportions of circulating B cells but two of them had a decreased proportion of CD4-positive helper-inducer T cells. We consistently found a severely impaired in vitro proliferative lymphocyte response to the plant lectin pokeweed mitogen (PWM). This could not be overcome by using suboptimal or supraoptimal doses of PWM, or by adding recombinant interleukin 2. In vitro PWM-induced IgM production was absent or low in two of the three patients studied and this low production could not be increased by addition of hydrocortisone. T lymphocytes responded normally to the plant lectins phytohemagglutinin and concanavalin A. T cells preactivated with phytohemagglutinin also normally proliferated in response to interleukin 2. It has previously been shown that lymphocyte activation with PWM involves both B and T cells and proceeds via an alternative pathway. The data thus indicate that patients with Bloom's syndrome have a specific defect in this PWM-induced alternative pathway of lymphocyte activation.

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Bloom's syndrome is a rare disorder with autosomal recessive inheritance. The major clinical manifesta-

tions are marked prenatal and postnatal growth retardation, a peculiar physiognomy, sunlight sensitivity, and hypogonadism.2 Increased sister chromatid exchanges,3 chromosomal instability, and a retarded DNA chain growth are the typical in vitro findings4 demonstrable in cultures of lymphocytes and fibroblasts. We have previously reported on the possible pitfalls in the clinical diagnosis of Bloom's syndrome.2 In the present report, an extensive immunological study was undertaken to better define the lymphocyte defect that predisposes patients with Bloom's syndrome to infections and malignancies.5

SUBJECTS AND METHODS

Four patients with Bloom's syndrome had diagnosis of their condition confirmed by the increased incidence of sister chromatid exchange in lymphocyte cultures. ²⁻³ Clinical details are shown in Table 1. Tests were performed simultaneously on blood from a patient with Bloom's and from one or two age-matched healthy controls. Blood samples were drawn after informed consent was obtained. Peripheral blood mononuclear cells (PBMC) were isolated from heparinized blood according to standard techniques.

Immunofluorescence

Staining for immunofluorescence analysis was performed as previously reported,6 and cells were analyzed on a cytofluorograph (FC 200, Ortho, Westwood, Mass, or a FACS-star, Becton Dickinson, Sunnyvale, Calif). Monoclonal antibodies to the CD3. CD4, CD8, CD16, CD19 and Ia antigens were used (Coulter Corporation, Hialeah, Fla, or Becton Dickinson, Mountain View, Calif). These antibodies detect surface antigens that are present on all T cells (CD3), helper-inducer T cells (CD4), suppressorcytotoxic T cells (CD8), natural killer cells (CD16), or B cells (CD19).7 Anti-Tac monoclonal antibody detects human lymphocyte interleukin 2 (IL-2) receptors.8

Cell Culture

Lymphocyte proliferation and IL-2 production in response to mitogens were measured as previously reported. 9,10 Interleukin 2 activity was tested on an IL-2-dependent mouse cytotoxic lymphoid line.11 To study IL-2-dependent proliferation of preactivated T cells, 2×10^6 PBMC were cultured in 6-mL snap-cap test tubes containing 1 mL of culture medium with phytohemagglutinin (PHA) (0.5 mg/L). After 120 hours, cells were washed twice and were resuspended at a concentration of 0.5×10^6 viable cells/mL. Cells were further cultured alone or in the presence of recombinant IL-2 (rIL-2) (Janssen Chimica, Beerse, Belgium) (10 IU/mL). After 24 hours, tritiated thymidine was added for four hours, cells were transferred to filter papers with a cell harvestor, and radioactivity on the filter papers was counted. Interleukin 2-receptor expression after 48 hours of culture with mitogens was measured with the anti-IL-2 receptor antibody.8 To study Ig production, 0.5×10^6 PBMC were cultured in a 1-mL volume, without or with pokeweed mitogen (PWM) (0.5 mg/L). After seven days, IgM in the supernatant was determined with an enzyme-linked immunoabsorbent assay technique as previously described.12 To eliminate suppressor cell activity, hydrocortisone (10-6M) (Sigma Chemical Co, St Louis) was added to some of the cultures.18

RESULTS

Results are given as means \pm SEMs. Statistical significances were calculated with the Mann-Whitney U test on unpaired samples.

As shown in Table 1, all patients had low serum levels of IgM and in three of them serum IgM was below the 95% confidence interval compared with age-matched controls. If In addition, one of them had decreased levels of IgA and another one had decreased IgG concentrations. In contrast, pro-

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| Table 1.—Clinical Data and Serum Immunoglobulin Levels* | | | | | | | |
|---|---------------------|---|---|----------------------------|--|--|--|
| | Patient 1, F | Patient 2, F | Patient 3, M | Patient 4, M | | | |
| Age, y | 21/2 | 51/2 | 8 | 24 | | | |
| Birth weight, g | 1550 | 1770 | 1500 | 1300 | | | |
| Birth length, cm | 40.5 | 44 | 40.5 | 30 | | | |
| Head circumference at birth, cm | 30 | *** | 29 | | | | |
| Presenting symptom | Failure to thrive | Failure to thrive | Failure to thrive | Short stature | | | |
| Age at diagnosis | 3½ mo | 13 mo | 6 y 2 mo | 15 y 4 mo | | | |
| Weight at diagnosis, kg | $2.4 (P_3 = 4.7)$ | $4.7 (P_3 = 8)$ | $9.6 (P_3 = 16)$ | 25.8 (P ₃ = 43) | | | |
| Length at diagnosis, cm | $50.2 (P_3 = 57)$ | 64.7 $(P_3 = 70)$ | 90.2 (P ₃ = 106) | 138 (P ₃ = 154) | | | |
| Head circumference at diagnosis, cm | $34.5 (P_3 = 38.5)$ | 39.5 $(P_a = 44)$ | $45.2 (P_3 = 49.4)$ | 49.5 (P ₃ = 52) | | | |
| Increased sister chromatid exchange in % of cells | 100 | 90 | 100 | 77 | | | |
| Infections | Upper airway | Middle ear; gastrointestinal; eyelids | Middle ear; gastrointestinal; eyelids | Upper and lower airway | | | |
| Serum immunoglobulin | | | | | | | |
| IgA, g/L (% nl) | 0.45 (66) | 0.42 (40) | 1.0 (69) | 2.36 (177) | | | |
| IgG, g/L (% nl) | 8.69 (117) | 10.64 (108) | 4.88 (47) | 9.09 (79) | | | |
| IgM, g/L (% nl) | 0.37 (42) | 0.38 (36) | 0.42 (41) | 0.72 (64) | | | |

^{*}Serum immunoglobulin levels were determined by a standard nephelometer assay. The values between parentheses refer to the age-related reference values (geometric means). Values below the 95% confidence interval are italicized. P₃ indicates third percentile; nl, normal.

portions of circulating B cells were normal or elevated (Table 2). Two patients also had decreased proportions of CD4-positive helper-inducer T cells. Proportions of CD8(+) suppressor/cytotoxic T cells and of Fcγ receptor-positive natural killer/killer cells (CD16-positive) were normal.

As demonstrated in Table 3, the proliferative response of lymphocytes to optimal concentrations of the T-cell mitogens (PHA) and concanavalin A (Con A) was not different from control responses. Moreover, PHA-activated T cells of patients with Bloom's syndrome proliferated normally in response to IL-2. Indeed, when T cells were preactivated by culturing PBMC with PHA for five days, then washed and additionally cultured with rIL-2 for 24 hours, IL-2-driven T-cell proliferation was normal (Table 3). The proliferative response of lymphocytes to an optimal dose of PWM, however, was significantly reduced (Table 3). Pokeweed mitogen is different from the two other mitogens used in that it activates both T and B cells15,16 and because it activates T cells via an alternative pathway. 10 Several experiments were therefore set up to further define the defect in lymphocyte activation with PWM in patients with Bloom's syndrome. First, when different concentrations of PWM ranging

| | Table 2.— | -Periph | | | (%) in Pa Subjects | ith Blo | om's | The state of the s |
|---|-----------|---------|------|------|-----------------------|---------|------|--|
| _ | | | | | | | | æ |

| Lymphocyte Marker | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Controls† |
|------------------------------------|-----------|-----------|-----------|-----------|-----------|
| CD3 (T cells) | 62 | 53 | 48 | 75 | 69±7 |
| CD4 (helper-inducer T cells) | 37 | 23 | 26 | 43 | 49 ± 9 |
| CD8 (suppressor-cytotoxic T cells) | 22 | 20 | 16 | 22 | 18±6 |
| CD4/CD8 ratio | 1.7 | 1.1 | 1.6 | 1.9 | >1.5 |
| CD16 (natural killer cells) | 28 | 8 | 5 | 28 | |
| CD19 (B cells) | 21 | 23 | 13 | 18 | 12±5 |
| HLA-DR | 28 | 23 | 15 | 20 | 14±5 |
| Lymphocyte count number (per mm³) | 6687 | 4442 | 1253 | 1760 | |

^{*}Lymphocyte subpopulations are expressed in percent of lymphocytes, and were determined by indirect immunofluorescence with monoclonal antibodies. Values 2 SDs above or 2 SDs below the mean of the controls are italicized. The values for patients 1, 2, and 3 are the mean of at least two determinations on different occasions. HLA indicates human leukocyte antigen.

from suboptimal to supraoptimal doses (0.005 mg/L, 0.5 mg/L, and 5 mg/L) were used, significant differences (P < .02) between the lymphocyte proliferative responses of patients and controls were found for each PWM concentration tested (not shown). When exogenous rIL-2 was added, no enhancement of PWMdriven tritiated thymidine incorporation was noted. This is shown in Table 4 for an optimal concentration of PWM (0.5 µg/mL). Similar results were also for lower (0.005 and obtained 0.05 mg/L) and higher doses of PWM (5 mg/L) (not shown). In contrast to our findings on defective PWM-in-

duced lymphocyte proliferation, it is shown in Table 5 that IL-2 production and IL-2-receptor expression in response to PWM were normal in patients with Bloom's syndrome. The T cells were also able to produce IL-2 and to express IL-2-receptors in response to triggering with PHA and Con A (not shown). Finally, PBMC were stimulated in vitro with PWM to measure IgM production (Table 6). Lowered IgM production was found in two of the three patients studied. Addition of hydrocortisone to the cultures to eliminate suppressor-cell activity13 did not reverse the low IgM production in these two patients.

[†]Controls included 15 healthy children age 1 to 13 years

Table 3.—Lymphocyte Proliferation in Response to Optimal Doses of Mitogens and to Interleukin 2 (IL-2) in Patients With Bloom's Syndrome and in Controls

| Adams (1) 15 September 1 | Tritiated Thymidine Incorporation, cpm | | | | | | |
|-----------------------------|--|----------|---------------------|---------------------|-------------------------|-----------------------|--|
| | | Medium | PHA* (0.5 mg/L) | Con A† (6 mg/L) | PWM* (0.5 mg/L) | IL-2† (10 U/mL) | |
| | 1 | 246 | 28 593 | 23 956 | 2794 | 42 202 | |
| Patient | 2 | 282 | 38 604 | 15 535 | 6704 | 29 758 | |
| ratient | 3 | 367 | 47317 | 10 969 | 3915 | 29 926 | |
| | 4 | 119 | 37 470 | 35 187 | 2756 | 39 606 | |
| Controls (n = 6) | | 396 ± 69 | 42 835 ± 1769 NS | 26 920 ± 4914 NS | 14 156 ± 1759 P<.02‡ | 44 533 ± 17 830 NS | |

*Peripheral blood mononuclear cells (0.5 × 10° cells/mL) were cultured in round-bottomed microculture plates for three days with optimal doses of mitogens. To quantify cell proliferation, tritiated thymidine incorporation during the last eight hours of culture was measured. Results for each patient represent the mean tritiated thymidine incorporation of quadruplicate cultures. For the control group, the means ± SEMs are presented.

†Peripheral blood mononuclear cells were preincubated with phytohemagglutinin (PHA) for five days, washed, and further cultured with recombinant IL-2. Tritiated thymidine incorporation was measured during the last four hours of culture. Values presented are tritiated thymidine incorporation in the presence of IL-2 after subtraction of tritiated thymidine incorporation in the absence of IL-2. Con A indicates concanavalin A; PWM, pokeweed mitogen; NS, not significant.

‡Patients vs controls, derived with a Mann-Whitney U test.

Table 4.—Recombinant Interleukin 2 (rIL-2) Does Not Restore Defective Response of Bloom's Syndrome Lymphocytes to Pokeweed Mitogen (PWM)*

| | PWM Concentration | Tritiated Thymidine Incorporation, cpm | | | |
|------------|----------------------|--|----------------------|--|--|
| | (mg/L) | No addition | With rlL-2 (10 U/mL) | | |
| Patient 1 | S 0 | 227 | 2468 | | |
| , anont i | 0.5 | 2365 | 2164 | | |
| Patient 2 | ∫ 0 | 325 | 1232 | | |
| , audin 2 | 0.5 | 6704 | 7281 | | |
| Patient 3 | ∫ 0 | 164 | 229 | | |
| i audiit J | 0.5 | 5313 | 5252 | | |
| Patient 4 | ∫ 0 | 119 | 418 | | |
| I GUSTIL 4 | 0.5 | 2756 | 2511 | | |

*Peripheral blood mononuclear cells from patients with Bloom's syndrome were cultured with PWM, in the presence or absence of rIL-2. After three days of culture, tritiated thymidine was added for eight hours. Results represent the mean tritiated thymidine incorporation in quadruplicate cultures.

COMMENT

Patients with Bloom's syndrome have an increased susceptibility to infections and a high predisposition to malignancy.5 These observations have led to the immunologic evaluation in search for possible defects in the host defense mechanisms. Decreased serum levels of immunoglobulins, impaired lymphocyte proliferative responses to mitogens, depressed in vitro production of immunoglobulins in response to PWM, and a defect in natural killer cell function have previously been found. 17-20 Our present data confirm immune defects in patients with Bloom's syndrome. The most consistently found manifestation of lymphocyte dysfunction was an impaired

in vitro lymphocyte proliferative response to PWM. This was found to contrast with normal PHA and Con A-induced T-cell responses. Hütteroth et al¹⁷ have also shown that the impaired lymphocyte proliferation in patients with Bloom's syndrome was most pronounced when PWM was used as a mitogen.

A potential explanation for the discrepancy between normal PHA/Con A-induced responses on the one hand and defective PWM-induced proliferation on the other hand can be provided by the recently acquired insight in the process of T-cell activation. T cells are activated by cross-linking the CD3-T cell receptor (TCR) complex on the membrane. This results in calcium influx, the appearance of IL-2-

receptors, IL-2 production, and IL-2dependent T-cell proliferation. 21,22 Both PHA and Con A interact with the CD3-TCR complex for transmembrane signaling, 23,24 and they induce an IL-2-dependent pathway of lymphocyte proliferation.21 However, PWM does not have to interact with the CD3-TCR to induce tritiated thymidine incorporation. The latter occurs via an "alternative" pathway of lymphocyte activation and proliferation in a calcium and IL-2-independent manner. 10,22 Although interaction of PWM with the CD3-TCR complex results in IL-2 production,10 IL-2 does not contribute to PWM-induced lymphocyte proliferation. 10 Moreover, PWM is able to activate both T and B lymphocytes. 12,16 Thus, if we reconsider in this context the data of our article, it appears that all functions that are induced via CD3-TCR signaling were normal in patients with Bloom's syndrome, including PHA and Con Ainduced lymphocyte activation and PWM-induced IL-2 production. In this respect it is interesting to note that in the one patient tested, we found a normal antigen-induced lymphocyte proliferation (J.L.C., unpublished data, 1987). Functions induced by PWM that are independent of the CD3-TCR complex (lymphocyte proliferation and Ig production by B cells) were found to be defective. Our results obtained with lymphocytes from patients with Bloom's syndrome thus are compatible with a specific defect in the alternative PWM-driven pathway of lymphocyte activation.

The defect might result from the absence or decreased density of a PWM-receptor on the lymphocytes. A receptor for PWM, however, has never been identified on lymphocytes.25 It could be argued that a specific defect in PWM-induced lymphocyte proliferation points to a selective defect in the B-cell function. However, tritiated thymidine incorporation was measured at day 3 of culture, at which time it largely reflects T-cell proliferation.26 Therefore, it is unlikely that the defective lymphocyte proliferation is due to a B-cell defect only. Our attempts to normalize the response to PWM by increasing or decreasing the mitogen concentration in the cultures, or by

Table 5.—Interleukin 2 (IL-2) Production and IL-2-Receptor Expression in Response to Pokeweed Mitogen (PWM) in Patients With Bloom's Syndrome and in Controls

| | | IL-2 Production (U/mL)* | % of IL-2-Receptor-Positive Cells† |
|------------------------|----|-------------------------|------------------------------------|
| | [1 | 2.90 | 11 |
| D-414 | 2 | 1.50 | NT |
| Patient | 3 | 4.32 | NT |
| | 14 | 4.86 | 32 |
| Controls (n (mean ± | | 5.67 ± 2.14 | 14 ± 3.47 |

*Interleukin 2 was measured in the supernatant of $1 \times 10^{\circ}$ cells/mL after 24 hours of culture with PWM 0.5 mg/L. Spontaneous production in the absence of PWM was <0.02 U/mL.

†Interleukin 2-receptor expression was measured after 48 hours of culture with PWM (0.5 mg/L) by determining the percent of IL-2-receptor-positive cells in indirect immunofluorescence. Less than 3% of unstimulated cells expressed IL-2-receptors. NT indicates not tested.

Table 6.—Spontaneous and Pokeweed Mitogen (PWM)–Induced IgM Production In Vitro by Lymphocytes of Patients With Bloom's Syndrome and in Controls*

| | | Spontaneous, ×10⁻⁴ g/L | PWM (0.5 mg/L), ×10 ⁻⁶ g/L | PWM and Hydrocort (10-* M), ×10-* g/L |
|------------------|----|------------------------|--|---------------------------------------|
| | [1 | <20 | 20 | <20 |
| Patient | 2 | 26 | 891 | 2281 |
| | (3 | <20 | <20 | 271 |
| Controls (n = 4) | | <20-109 | 369-2056 | 873-8953 |

*Peripheral blood mononuclear cells (0.5 × 10°/mL) were cultured in a 1-mL volume, without or with PWM (0.5 mg/L). After seven days of culture, the supernatants were collected and igM was measured by enzyme-linked immunoabsorbent assay. Results are the mean of duplicate cultures.

adding exogenous IL-2 were unsuccessful. Addition of IL-2 also had no effect at all on PWM-induced lymphocyte proliferation. This might be surprising in view of the IL-2-receptor expression on PWM-activated T cells. However, it has recently been shown that Tac expression does not necessarily imply the presence of functional IL-2-receptors on the membrane.

A retardation in the rate of DNA replication fork movement⁴ and a slower cell proliferation^{28,29} have been shown in both fibroblasts and lymphocytes from individuals with Bloom's syndrome. We therefore should consider an intrinsic defect in S phase DNA synthesis as the explanation of the lymphocyte dysfunction. This, however, is not supported by our findings that the lymphocytes incorporated tritiated thymidine in response to PHA, Con A, and IL-2 to a degree not different from the results in controls.

We further found a low IgM production in vitro in response to PWM in two of the three patients studied, which is in accordance with previous reports. 17-19 Low IgM production can-

not be ascribed to increased suppressor T-cell activity, because addition of hydrocortisone (specifically eliminating suppressor-cell activity in vitro13) did not normalize the response. Pokeweed mitogen-induced immunoglobulin production by B cells is dependent on the secretion of helper factors by T cells,30 including IL-2.31 Pokeweed mitogen-induced IL-2 production was normal in patients with Bloom's syndrome, but other helper factors for B cells have not been measured. Therefore, further studies are required to find out whether the reported defect in in vitro PWM-induced immunoglobulin production is due to a B cell dysfunction or to a quantitative and/ or functional T cell defect, or to a combination of both. Data from Taniguchi et al19 support the latter expla-

In summary, our data show that PWM-induced lymphocyte proliferation and Ig production in vitro are defective in patients with Bloom's syndrome. This probably does not relate to the intrinsic defect in semiconservative DNA replication observed in this syndrome, but might result from

defective transmembrane or intracellular signaling in lymphocyte activation. The relevance of this in vitro finding to explain clinical signs of immune dysfunction with increased susceptibility to infections and increased incidence of malignancies⁵ awaits further elucidation of the importance of this alternative pathway.

We thank Dr T. Waldmann (National Institutes of Health, Metabolism Branch, Bethesda, Md) for providing the monoclonal anti-Tac antibody, and Nele Nuyts for secretarial assistance in the preparation of this manuscript.

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Book Review

Assuring Quality Out-Patient Care for Children, by Charles D. Cook and Jane Heidt, 204 pp, New York, Oxford University Press, 1988.

Dr Cook and Ms Heidt have written a book that synthesizes ten years of effort directed toward improving the quality and containing the cost of health care for children. This documentation of their work is thoughtful and painstaking. The book begins with three brief chapters, giving an overview of the problem. The first details the intimidating magnitude of their quest. The second and third chapters document problems in health care provision and review briefly past experience with efforts at quality assurance. Can two different health care facilities differ threefold to tenfold in their rates of performance of diagnostic tests or therapeutic endeavors and each still represent quality care at reasonable cost?

The remaining 85% of the book is devoted to a detailed description of the Pediatric Guidelines Medical Information System (PGMIS) now in place at six New York City municipal hospitals and one voluntary hospital. As the authors note, quality assurance ventures to date have tended to focus on structure or process, with efforts at outcome assessment now beginning to take form. The project described in this monograph centers squarely on assessment of process.

The authors assert that ten common pediatric problems comprise about "80% of acute care pediatric ambulatory visits nationwide." For these ten problems, they have developed guidelines that embody "standards for the optimal care of common ambulatory pediatric problems." Their PGMIS, then, consists of computer-assisted auditing of outpatient records to determine the degree of adherence by physicians. Monthly reports are generated for individual physicians and for their physician supervisors. By enumerating compliance with the guidelines, the monthly reports presumably allow assessment of the quality and cost-effectiveness of care rendered.

As the authors themselves note, "the guidelines are the sine qua non of the system." So, too, one's assessment of the merit of their PGMIS must begin with a critical evaluation of those guidelines. As a practitioner in a busy ambulatory department of a children's hospital, I find the guidelines faulty in several specific respects. Notwithstanding the authors' caveats that these guidelines do not apply to all cases, the guidelines contain some questionable positions regarding optimal care. Some elements of the guidelines with which I would differ are as follows: (1) the

diagnosis of an upper respiratory tract infection cannot be given to a child with a temperature higher than 39°C; (2) a throat culture is required when the rapid streptococcal antigen detection test result is positive; (3) in a child with typical croup, with mild or absent respiratory distress, admission is mandated when the temperature is 39°C or higher and the white blood cell count is higher than $15\times10^{\rm s}/\rm L$; and (4) a child with otherwise typical viral pneumonitis must be admitted if the neutrophil count is lower than $1\times10^{\rm s}/\rm L$.

In general, the fault I find with these guidelines is that they place excessive reliance on degree of fever and results of white blood cell counts, far beyond the discriminating ability of those items to dictate diagnosis or beneficial therapy. I am surprised that these guidelines could be the result of years of revision and consultation with numerous experts.

In support of the specific guidelines, the authors offer two expository chapters. One contains decision trees, which, in this instance, are nothing more than diagrammatic reiteration of the guidelines' text. They are better described as algorithms, since they lack the explicit quantitative estimates that comprise the logic of decision trees. The other chapter provides annotations to the guidelines, citing 127 articles to support the judgments made. I was disappointed to find little in this chapter that addressed my specific concerns as sampled above.

This book is indeed impressive in the scope of its endeavor and its attention to details of implementation. It deserves careful reading by anyone engaged in quality assurance of pediatric care. Surely commendable is the development of a system that permits regular collection of complete clinical data, automated evaluation of that data, and continual feedback to physicians regarding their performance. It seems that such a system cannot help but improve the adherence by practitioners to the clinical guidelines. Whether it leads also to improvements in quality of care or cost containment, however, depends first on the adequacy of the guidelines and standards and on their acceptance by a wide audience of pediatricians. On this point, I believe, Dr Cook and Ms Heidt have additional work ahead.

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Necrotizing Tracheobronchitis

An Ischemic Lesion

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 Neonates with necrotizing tracheobronchitis present a diverse clinical spectrum from asymptomatic disease to severe airway obstruction. A retrospective clinicopathologic study of 206 neonatal autopsy reports spanning a three-year period yielded 122 cases of necrotizing tracheobronchitis with an incidence of 59%. All study patients received treatment prior to the development of high-frequency ventilator jet, oscillator, or interruption. The site and submucosal depth of airway involvement was variable. The most commonly affected anatomic site was the middle or thoracic trachea (56%). The common cause identified was severe ischemia to the airway mucosa and submucosa, occurring with profound birth asphyxia and/or shock. The presence of ischemia supports the concept that decreased tracheoperfusion may be an important factor in the development of tracheobronchial abnormalities.

(AJDC 1988;142:1094-1098)

Necrotizing tracheobronchitis (NTB) has been reported as a complication related to mechanical ventilation in infants with respiratory failure.1-10 Since 1979, in our institution, an increasing number of neonatal autopsy reports have noted the presence of NTB characterized by replacement of normal tracheal mucosa with acute inflammatory cells, mostly neutrophils. In addition, the airway lumen often contained necrotic debris. Clinically, the diagnosis of NTB was entertained only occasionally in situations presenting as difficult ventilation, increasing mucoid secretions, and airflow obstruction.

The unexpected and often silent

presentation of NTB and its potential consequences for the survivors led to a retrospective study of all neonatal autopsies for the years 1979 through 1981. Questions concerning frequency of occurrence, clinical presentation, and possible causal factors of NTB were examined. The purpose of this communication is to report the results of this study, with particular emphasis on the pathologic findings and the possible role of ischemia as a causal factor.

PATIENTS, MATERIALS, AND METHODS Population Studied

We reviewed the medical and autopsy records of all the neonates who had required conventional mechanical ventilation from Jan 1, 1979, through Dec 31, 1981. All infants were cared for in the Newborn Center of The Children's Hospital, Denver (a regional referral center for newborn intensive care). During the study period, there were 2148 newborn admissions, and 1403 of these infants required ventilatory assistance for respiratory failure due to a number of primary respiratory problems. There were 281 neonatal deaths (13.1%), and autopsy studies were performed in 206 cases.

The records of all patients were reviewed and pertinent antenatal, intrapartum, neonatal, and postmortem information was collected. The information gathered from each record included the following: sex, birth weight, gestational age; complications of pregnancy, labor, and delivery; Apgar scores; type and severity of respiratory distress; ventilatory support required; route and duration of endotracheal intubation; pulmonary roentgenographic findings; presence and severity of shock; pharmacologic support required; and any culture specimens obtained and results.

Upper Airway Histopathologic Studies

Routine specimens obtained at necropsy included the following: a longitudinal laryngotracheal section traversing the epiglottis, true and false vocal cords, and 3 to 5 cm of proximal trachea; a coronal section

of distal trachea at the level of the carina; and a pulmonary hilar sample with mainstem and lobular bronchi represented. The material was fixed in a buffered neutral 4% formaldehyde solution, embedded in paraffin, sectioned at 6 µm, and stained with hematoxylin-eosin.

The diagnosis of neonatal NTB was based on histologic review, noting alterations of normal tracheal mucosa and submucosa. All pathologic specimens originally were examined and described by one of three pediatric pathologists and later reviewed by one pathologist for confirmation of specific tracheal abnormalities.

Mild epithelial changes like loss of cilia and squamous metaplasia were not included in the current grading system. We employed a slight modification of the approach of Joshi et al¹ to tracheal histopathology. Grade 1 indicated mucosal necrosis only (Fig 1). Grade 2 included both mucosal and submucosal necrosis, often characterized by submucosal basophilia and loss of surface epithelium (Fig 2). Grade 3 described marked mucosal and submucosal necrosis with a mild to moderate inflammatory infiltrate. If the inflammation was severe, the subdesignation "S" was added (Fig 3). If perichondritis was observed, the subdesignation "C" was added (Fig 4). As anticipated, occasional laryngeal ulcers were associated with subjacent inflammation of the arytenoid or cricoid cartilage. Unanticipated, however, was the antiluminal perichondritis occasionally observed in the distal trachea or mainstem bronchi. sometimes in regions demonstrating only grade 2 submucosal changes.

Several recent studies have employed other histopathologic features and different grading systems of upper airway damage related to high-frequency ventilatory effects.^{2,3} For the sake of simplicity, we regarded the three-grade system as sufficient. The infants in our study did not have tracheal or bronchial occlusion by sloughed mucosa or submucosal tissue, although some infants exhibited substantial fibroproliferation impingement of airway lumina

Twenty-five cases of NTB were selected at random and studied in depth. Of the sampled anatomic sites, three autopsies lacked laryngeal sections, two showed no

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Fig 1.—Type 1 lesion, proximal trachea. Submucosa is intact and uninflamed. Mucosa is necrotic and partially detached (arrows) (hematoxylin-eosin, original magnification × 40).

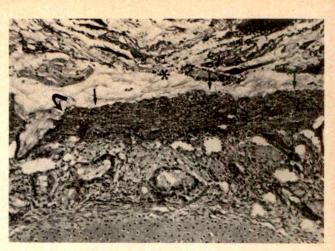


Fig 3.—Type 3 lesion. Distal trachea with extensive mucosal ulceration (straight arrows), submucosal necrosis, and inflammation (bent arrow). Tracheal glands are dilated. Tracheal lumen, at top, is partially occluded by pseudomembrane of denuded mucosa, mucus, and neutrophils (asterisk) (hematoxylin-eosin, original magnification × 40).

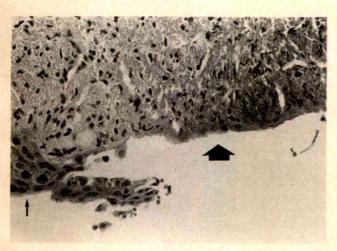


Fig 2.—Type 1/type 2 lesion interface. Distal trachea. Intact mucosa (small arrow) abuts ulcerated region. Wide arrow (on right) points to type 2 lesion with necrotic, basophilic submucosa (hematoxylin-eosin, original magnification × 100).

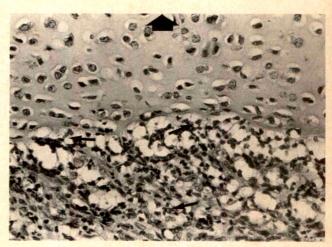


Fig 4.—Type 3C lesion. Trachea carina. Perichondritis with neutrophils (thin arrows) involving distal tracheal ring on antiluminal surface. Thick arrow indicates direction of lumen (hematoxylineosin, original magnification × 100).

epithelial alterations of the larynx, two evidenced grade 1 changes, and 12 had grade 2 changes. Five laryngeal alterations were grade 3, four of these with associated chondritis and three with severe inflammation. One baby had marked submucosal fibrosis. Duration of intubation was similar for all babies.

Tracheal alterations were significantly worse, with 23 infants manifesting grade 3 lesions, 15 with severe inflammatory component, and five with substantial perichondritis. One baby had striking submucosal fibroproliferation. Only two infants had grade 2 tracheal changes. No entirely normal tracheal mucosa was found and no simple grade 1 lesions were seen. Sampled bronchi revealed 13 without abnormalities.

two with grade 1 changes, and three with grade 2 changes. Seven infants had grade 3 alterations of their bronchi, four with severe inflammation, three with perichondritis, and one had obliterative fibroproliferation.

Statistical Analysis

Data were analyzed for significance with a two-tailed t test. A P value of <.05 was considered significant.

RESULTS Incidence of NTB

During the study period, 206 neonatal autopsies were performed. The presence of NTB was noted in 122 cases, an incidence of 59%.

Population Profile

Table 1 shows some of the obstetric and neonatal factors evaluated in all of the autopsied cases. Both groups, with and without (control) NTB, were strikingly similar. All patients were intubated and received conventional ventilator therapy that consisted of oral intubation, positioning of the endotracheal tube tip in the high midtrachea (confirmed by roentgenogram), and uniform gaseous humidification (body temperature, 36.5°C). All patients received 100% fraction of inspired oxygen increased from 60% to 100% fraction of inspired oxygen to

| Table 1.—Study Cases: Population Profile* (n=206) | | | | | |
|---|------|---------------------------|----|-------------------|---------|
| | Trac | otizing heitis, (%) | | entrol, o. (%) | P Value |
| Obstetric factors PROM | 10 | (8) | 7 | (8) | 0.972† |
| Premature labor | | (16) | | (16) | 0.833† |
| Fetal distress | | (0.8) | | (1.2) | 0.789† |
| Abruptio, previa | 7 | (6) | 7 | (8) | 0.467† |
| Neonatal factors Hypotension | 24 | (20) | 4 | (4.8) | 0.002 |
| HMD | 61 | (50) | 32 | (38) | 0.910† |
| Pneumonia | 2 | (1.6) | 4 | (4.8) | 0.190† |
| PPHN/lung hypoplasia | 14 | (12) | 9 | (11) | 0.864† |
| Meconium aspiration | 2 | (1.6) | 2 | (2.4) | 0.704† |
| PIE | 23 | (19) | 12 | (14) | 0.391† |
| Pneumothorax | 38 | (31) | 22 | (26) | 0.442† |
| IVH | 41 | (33) | 20 | (24) | 0.130† |
| BPD | 7 | (5.7) | 1 | (1.2) | 0.096† |
| Sepsis | 15 | (12) | 7 | (8) | 0.365† |
| Total± | 122 | (59) | 84 | (41) | |

^{*}PROM indicates premature rupture of membranes; HMD, hyaline membrane disease; PPHN, persistent pulmonary hypertension of newborn; PIE, pulmonary interstitial emphysema, IVH, intraventricular hemorrhage; and BPD, bronchopulmonary dysplasia.

[†]Not significant ‡The discrepancy in the final totals is a result of more than one factor being present in a particular patient.

| Table 2.—Incidence (%) of Necrotizing Tracheobronchitis in Autopsy Cases by Days of Intubation* | | | | | | |
|---|-----------|---|--|--|--|--|
| Days Ventilated | Autopsies | Necrotizing Tracheobronchitis,† No. (%) | | | | |
| 1-5 | 160 | 89 (55.6) | | | | |
| 7-13 | 20 | 14 (70.0) | | | | |
| ≥14 | 26 | 19 (73.0) | | | | |
| Total | 206 | 122 (59.2) | | | | |

^{*}From The Children's Hospital, Denver, 1979 to 1981.

maintain an arterial oxygen saturation of 90% or more. Positive end-expiratory pressure of 4 to 6 cm H₂O was used to improve oxygenation. Mean airway pressure was not examined. Ventilatory pressures were similar: 26/6 vs 25/6 (11 patients counted in each group). Duration of intubation was similar in each group (Table 2).

The only factor that statistically was found to be significant was hypotension (defined as a mean arterial pressure of less than 15% or more below normal range for one hour).11 Twenty percent (24/122) of babies with NTB had marked hypotension in the neonatal period, as compared with 4.8% (4/84) of babies without NTB (P < .002).

Apgar Score and NTB

The frequency of NTB in autopsy cases was examined in relation to Apgar scores at one and five minutes (Table 3). Necrotizing tracheobronchitis was found more often in infants with lower Apgar scores. It was found in 38 (77.6%) and 40 (50.6%) infants with a five-minute Appar score of 0 to 3 and 7 to 10, respectively. This difference was statistically significant at P < .011. In addition, it is worth noting that in infants with a five-minute Apgar score of 7 to 10, 20 of 40 infants with NTB developed profound hypotension during their hospital course, contrasted with three (7.7%) of 39 infants without NTB (P<.0006).

| | Tat | ile 3. | N | ecrol | izing | | |
|-------|-------|--------|------------|-------|------------|----|-----|
| Traci | heobr | onch | itis ir | ı Aul | opsy | Ca | ses |
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| | | | inute | | | | |

| | Autopsy Cases | Tracheo- bronchitis, No. (%) |
|--------------|------------------|------------------------------------|
| Total No. | 206 | 122 (59.2) |
| 1-min Apgart | | |
| 0-3 | 115 | 72 (62.6) |
| 4-6 | 52 | 30 (57.7) |
| 7-10 | 39 | 20 (51.1) |
| 5-min Apgar‡ | | |
| 0-3 | 49 | 38 (77.6) |
| 4-6 | 78 | 44 (56.4) |
| 7-10 | 79 | 40 (50.6) |

^{*}From The Children's Hospital, Denver, 1979 to 1981.

Anatomic Involvement and Histologic Findings

Figure 5 displays the primary site of involvement by NTB. The most commonly affected anatomic locale was the middle or thoracic trachea (56% [93/167]). Involvement of other areas varied: 20%, 15%, and 9% for the cervical trachea, carina, and mainstem bronchi, respectively. The preferential involvement of the midtrachea was statistically significant at P < .001.

NTB and Infection

Fifteen infants with NTB (12%) and seven infants without NTB (8%) had documented infection at the time of death. Only one baby with NTB had identifiable tracheal infection. Staphylococcus aureua and Pseudomonas aeruginosa were the organisms isolated from the trachea of this single infant.

COMMENT

In our series, the majority of patients with NTB had a silent clinical presentation, and in almost all cases, an unexpected one. Kirpalani et als recently reported that acute hypercapnia was associated with the presence of NTB, and that a silent clinical presentation was uncommon. The diagnosis of NTB clinically was entertained only occasionally in our unit during these years in situations presenting as difficult ventilation, increasing mucoid secretions, or airflow obstruction.

[†]P = .143.

[†]P = .446.

 $[\]pm P = .011$.

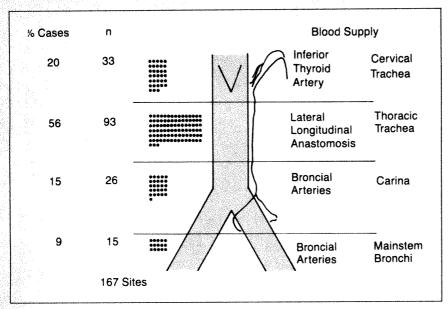


Fig 5.—Involvement site of necrotizing tracheobronchitis (122 cases).

All cases of NTB occurred in intubated neonates and, regardless of birth weight, an identical incidence was seen in both the smallest and largest neonates. As other studies have demonstrated, NTB is not solely a disease of the low-birth-weight infant.⁴⁷ Furthermore, NTB is not a new disease process as noted by Mammel and Boros.⁸

Duration of intubation did not correlate with the presence or severity of NTB. Routine humidification with inspired gas at body temperature was the standard of care in an attempt to maintain the normal upward flow of mucus

The role of infection, especially infectious tracheitis, was examined. In only one case of NTB was an infectious organism deemed important in pathogenesis. This finding is similar to that of other early investigators.¹¹

Previous reports stress certain observations that our study did not verify. The laryngeal region had been recognized as the most common site of trauma. Further, Joshi et al¹ noted a close correlation in the degree of involvement when both larynx and distal trachea were damaged. Our data do not support either of these observations. The majority of our patients manifested high-grade lesions in the midtrachea with variable involvement of the larynx.

The presence of the endotracheal

tube previously has been reported as the responsible factor in much of the laryngotracheal trauma. 1,7,8 Possible mechanisms of damage include direct pressure effect, its abrasion, respirator and transmitted piston effect, endotracheal tube irritant potential, and the possibility of toxin effect from the endotracheal plastics or cleanser. 13 Our data do not support these hypotheses. The trachea below the true vocal cords to approximately 1 cm above the carina was the region in our series with the most surface ulceration and damage, whereas the larynx was less significantly involved. This would argue against direct or transmitted pressure phenomena, since the tube is common to both locales but is more tightly positioned in the larynx. The distal trachea is exposed to intermittent trauma from suction catheters. Right and left mainstem bronchial damage might be secondary to this: however, a number of patients exhibited severe mucosal necrosis of lobular bronchi distal to where suction catheter contact could be implicated. Such findings are suggestive of a more generalized insult.

The description of the abnormality of NTB has been approached by different grading systems in several studies. ^{1,7} The subject has been addressed in a qualitative fashion as well, including gross and microscopic observations. These observations often re-

late sequential lesions with the duration of intubation. In this report, we have chosen the grading system of Joshi et al1 to describe the histopathologic condition with slight modification. We recognize that this system does not include the earliest and most subtle alterations in the tracheal epithelium, those of mucosal and submucosal edema and hemorrhage. These changes then progress to necrosis, inflammation, and ulceration, which are graded. Eventually, the involvement can be extensive enough to damage cartilage, which we have indicated by a "C." Reepithelialization can occur. A submucosal reparative phenomenon is occasionally seen, an admixture of granulation tissue and fibroproliferation that constricts the lumen of the airway.

On detailed examination of all cases of necrotizing tracheitis, the presence of ischemia as a common thread was noted, evidenced by low five-minute Apgar scores. In a significant number of patients, the five-minute Apgar score was in the range of profound asphyxia, 0 to 3. Furthermore, in 50% (20/40) of infants with necrotizing tracheitis, there was an associated Apgar score of 7 to 10, severe hypotension (mean arterial pressure 15% or more below normal range for one hour), and suspicion of sepsis or cardiogenic shock. Hypotension is not the major problem, but the ischemia that results is a most significant insult. Due to the rich anastomoses of vessels supplying the mucosal and submucosal tracheobronchial tree, asphyxia, hypotension, and subsequent ischemia would have a profound impact. The vascular supply of the cervical and upper thoracic trachea arises from the inferior thyroid artery. The midportion or thoracic trachea obtains its blood supply from the lateral longitudinal anastomoses that course along its lateral borders.14 Since these represent end-arterial blood supplies, they are susceptible to pressure changes and variations in oxygen saturation. This thoracic trachea is the site of major involvement with NTB. Such findings in the trachea with a tenuous vascular supply may be another example of a "watershed" susceptibility occurring with profound ischemia in neonates. Similar ischemic mechanisms are invoked in papillary muscle necrosis with tricuspid valve insufficiency and parasagittal neuronal injury in the central nervous system. 15-17

We also noted significant perichondritis, frequently on the antiluminal aspect of the distal trachea or near the carina and occasionally in the distal bronchi. Only one of five patients with inflammation of the tracheal cartilage rings had an associated luminal ulcer, and this patient also had laryngeal ulceration with inflammatory extension to the arytenoid cartilage plate. The presence of antiluminal chondritis and perichondritis without inciting organisms lends support to the suggestion of ischemia being causal in the entire necrotizing process. Such an insult could lead to focal cartilaginous necrosis and subsequent inflammation. Barotrauma, catheter incitants, and other luminal factors clearly are noncontributory in this antiluminal locale. Previous studies of airways have been directed at the mucosal and submucosal tissues with scant attention to the distal and antiluminal cartilage. The substantive chondritis noted in our patients may explain the tracheomalacia often noted in infants recovering from bronchopulmonary dysplasia. 16-18

The potential clinical implications for surviving neonates with NTB are significant. Tracheomalacia with abnormal conducting airway stability may well predispose the survivor to significant airway embarrassment and respiratory distress. 18-20 This tendency may have major implications for those infants with first-time exposure to the many respiratory viral pathogens. Do survivors with NTB have narrower upper airways and are they at an increased risk for laryngotracheobronchitis?

This report indicates that NTB occurs at least in part as a result of a more global insult such as ischemia rather than simply secondary to mechanical ventilatory support as previously believed.21,22 Mechanical ventilation can be a significant contributing factor for ischemia leading to NTB. One proposed theory for the role of mechanical ventilation and mean airway pressure in NTB introduces the concept of tracheal perfusion pressure (TPP). Tracheal perfusion pressure is the sum of two factors: mean arterial blood pressure (MABP) and mean airway pressure (MAP). These two forces would seem to oppose each other in terms of perfusion of the tracheal capillary bed. Not all neonates are the same gestational age; thus, some factor accounting for gestational age and airway stability should be considered. 18 Thus, the final equation representing TPP might be as follows: TPP = MABP - k(MAP), where k represents the "airway distensibility factor." With such a concept, ischemia secondary to hypoperfusion is the final common pathway of NTB. Hypoperfusion may be caused by a decrease in the MABP, increased MAP, or a combination of the two. Such a theory deserves further investigation and has precedent in other organ systems, specifically the central nervous system. A similar theory exists for cerebral perfusion: Cerebral perfusion pressure equals MABP minus intracranial pressure.23

The issue of high-frequency ventilation and the role it plays in NTB is of current interest. Recently, the contribution of high-frequency oscillatory ventilation has been shown to be no more damaging to the airway than conventional ventilation.24,25

In conclusion, NTB appears to be another pathologic entity that can be added to the spectrum of morbidities observed in the critically ill neonate who experiences respiratory failure requiring significant ventilatory support. Quite possibly, ischemia, either due to hypotension associated with birth asphyxia or shock or from excessive ventilatory pressure support/ mean airway pressure, plays a major role in the pathogenesis of NTB.

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The Effects of a Mandatory Child Restraint Law on Injuries Requiring Hospitalization

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 Using data on all inpatients in 16 Michigan hospitals from 1980 through 1985, the clinical effects of a mandatory child restraint law were examined. Timeseries analytic techniques revealed a 36% decline in hospitalization for all injuries, with a 25% decline for head injuries, and a 20% decline for extremity injuries for children younger than 4 years, in addition, length of stay declined for children hospitalized secondary to motor vehicle crashes. This study confirms the effectiveness of the child restraint law in Michigan, previously demonstrated by analyses of police records. Current hospital databases may be able to serve as one component for the implementation of comprehensive injury surveillance systems.

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Following the lead of Tennessee in 1978, every state has now implemented laws that require children in passenger cars to be restrained. Implemented in April 1982, Michigan's law allows the use of either a child restraint device (CRD) or seat belt, depending on age and seat position. Following implementation, restraint use by children under age 4 years increased from 12% to 51%.1 This increase in restraint use was accompanied by an overall decline of 25% in the number of injured children as indicated in police crash reports.1 Children in crashes involving low levels of vehicle damage experienced the largest decline (50%) while children in the most severe crashes experienced a decline of 22%.1

Although the overall effectiveness of Michigan's child restraint law is gratifying, it is also important to examine the effect on specific clinical types of injuries that have been most affected by child restraint use, particularly severe ones. For example, since motor vehicle crashes are a major cause of head injuries, 2,3 it is important to document that the CRD law has been associated with a decline in these injuries. Knowledge of specific types of injuries averted by the CRD law is also important in estimating savings in both short-term medical care costs and potential long-term disabilities.

Using hospital discharge data for the 27 months before and 45 months after implementation of the law, this report describes the effects of the CRD law on injuries to the head, neck, spine, thorax, abdomen, and extremities. Specifically, this study examines the association between the implementation of a mandatory restraint law, increased restraint use, and changes in motor vehicle child passenger injuries.

THE EFFECTIVENESS OF CHILD RESTRAINT DEVICES

During the late 1960s, investigators began to recognize the deficiencies of then-available CRDs.4 In April 1971, the first version of Federal Motor Vehicle Safety Standard 213 eliminated the most ineffective and dangerous seats, but tests of structural integrity in 30-mph crashes were performed only on a voluntary basis. This regulation was revised in 1981 to require testing of child restraints under dynamic impacts simulating a 30-mph crash. Forward-facing restraints are required to limit forward motion of the head and knees, as well as decelerations of the head and chest. Rearfacing restraints are required to limit the angular deviation from the vertical of the back and head support surface. In other words, CRDs are designed with particular attention to keeping the child's head from striking the vehicle interior while holding onto the child's body in a manner that will not itself induce injury.

Although numerous studies have documented the effects of CRDs using police crash records, 1,5-7 there are relatively few reports of the clinical consequences of CRD use. Agran and coworkers8 reviewed injuries of over 500 children under age 4 years brought to nine emergency rooms in southern California following motor vehicle crashes. Approximately half the cases occurred before the implementation of the law requiring CRD use in California. Whereas 26% sustained head injuries before the passage of the law, only 18% of those receiving emergency treatment after the law suffered head injuries. In addition, head trauma was less severe after the law's passage. The study reported no differences in injuries to the chest, abdomen, or extremities.

Hall and coworkers interviewed 2105 families involved in motor vehicle crashes over the course of one year in North Carolina. The purpose of their study was to validate police reports and to obtain more detailed information on the types of injuries and circumstances of the crashes. They reported that 2.2% of unrestrained children sustained serious head injuries or fatalities in contrast to 0.4% of the restrained children, a reduction of 81%. In the more severe crashes, restraints reduced serious head injuries and fatalities by 74%.

Although only 10%¹⁰ of children involved in crashes are hospitalized,

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statewide hospital data are useful for examining the clinical effects of the restraint law for two reasons. First, injuries requiring hospitalization are generally more serious than those treated in emergency rooms. A reduction in serious injuries is obviously the most desirable outcome of the restraint law. Second, it is unlikely that any single practice or even hospital would have a sufficiently large database to examine changes in total injury rates, much less particular types of injuries, such as to the head or extremities.

In summary, clinical studies have begun to confirm findings from analyses of police reports on traffic crashes. Implementation of mandatory child restraint laws has been associated with decreases in injury frequency and injury severity, specifically with regard to head injuries. A statewide hospital database provides the opportunity to document in greater detail the effects of increased child restraint use.

METHODS

The Michigan Inpatient Data Base (MIDB) provided the data for our analyses. These data, including all discharges from all Michigan hospitals, have been maintained by the Michigan Health Data Corporation since 1980, under the sponsorship of the Michigan Hospital Association. Among the variables abstracted from medical records for the MIDB are age of patient; dates of admission and discharge, diagnosis (primary and up to six secondary entries using the International Classification of Diseases, ninth revision, system); and hospital identifier. The state health department maintains a separate count of hospital discharges that indicates that approximately 2.5% of discharges do not get entered into the MIDB. These missing entries are from small hospitals without the resources to meet the time demands for entry into the annual MIDB file. To resolve discrepancies between MIDB and state data, the Michigan Health Data Corporation generates a random sample of discharges from the previous year for each missing hospital in question and enters those duplicates into that hospital's MIDB file

Since up to seven diagnoses are abstracted from the hospital records, it is possible to recover both the N code (nature of the injury) and the E code (external cause of the injury). However, in the entire state, only 10% of injury N codes have an

accompanying E code. Consequently, we have restricted our analyses to the discharges from 16 of the approximately 239 hospitals in the state that consistently reported E codes for greater than 80% of N codes indicating injuries. Discharges from these 16 hospitals constitute approximately 9% of all discharges in the state. These 16 hospitals have been used for two reasons. First, a change in reporting of motor vehicle-related injuries could mask any change in the underlying rates of injuries. Since these hospitals consistently recorded a high proportion of E codes, the potential for reporting biases has been substantially reduced. Second, hospitals that regularly use and record E codes are assumed to be more reliable reporters of external causes of injuries. Criteria used by hospitals to determine a particular E code are likely to remain relatively stable from one year to the next.

The 16 hospitals do not represent a random sample, but we are confident about the internal validity and generalizability of this sample. In terms of internal validity, referral patterns in these communities remained stable during the years 1980 through 1985. In the communities with more than one hospital, injury rates at the hospitals not included in our sample also declined. Specifically, the proportion of patients with injuries admitted to the ten hospitals analyzed in detail that shared catchment areas with 28 other hospitals remained stable from 1980 through 1985. The other six hospitals are the primary providers of hospital care in their geographic regions.11 In terms of generalizability, these hospitals represent a cross section of sizes and locations of institutions within the state. For example, five are large or moderately large urban hospitals, four are small rural hospitals, with the others in between. The sample does not include a preponderance of facilities with specialized trauma centers.

Since information on actual CRD use is not available, we have restricted cases to those that could have been affected by restraints. Therefore, the following E codes were excluded: (1) any E810 through E819 code with a .2, .3, .4, .5, or .7 fourth digit, which represents motorcyclists, passengers on motorcycles, occupants of streetcars, riders of an animal, bicyclists, and pedestrians, respectively; and (2) E817, which represents an injury associated with boarding or alighting from a motor vehicle. The injury outcomes are based on groupings of reported N codes into six anatomical regions: head, neck, back, thorax, abdomen, and extremities. (These codes are available from us on request.) To control for quality of reporting, only injuries reported as the principal diagnosis have been included in the analyses. The principal diagnosis is the reason for admission. To the extent that a small proportion of children had more than one injury, our estimates of the effects of the law are conservative.

Monthly rates of injury discharges for the years 1980 through 1985 were adjusted separately for three potential confounders. First, the crude rates were adjusted for population size since an increase or decrease in population could account for corresponding changes in monthly injury rates. Second, rates were adjusted for vehicle miles traveled because mileage traveled is a measure of exposure risk for a motor vehicle injury and is an important determinant of aggregate injury rates. For example, if the amount of travel mileage decreases, injury rates are likely to decrease as well, possibly masking the effects of a particular intervention, such as the implementation of a restraint law. Finally, crude rates were adjusted for the number of motor vehicle crashes. This final measure is probably the most rigorous test of the effects of the child restraint law because it is ultimately children involved in crashes who are affected by the use of CRDs and seat belts. Because population, vehicle miles traveled, and crashes are not available specifically for the catchment areas of the 16 hospitals, the three adjustments were made using the respective figures for the entire state. Use of the statewide figures assumes that they reflect changes in population, vehicle miles, and crashes in the catchment areas under study.

Effects of mandating the use of restraint systems on child injuries were examined using Box-Jenkins interrupted time-series intervention analyses. This method uses iterative Auto-Regressive Integrated Moving Average model identification, estimation, and evaluation techniques for analyzing time-series data, and can control for a wide variety of trend, seasonal, and other autocorrelation patterns. Compared with alternative analytic strategies, the Box-Jenkins methods more accurately account for time-series data regularities, as evidenced by lower residual error variances. 18,14

Most models included low-order moving average and first-order seasonal moving average parameters, operating on the seasonal differences of natural logarithm-transformed injury rates. Step functions were added to the Auto-Regressive Integrated Moving Average models to estimate the effects of the compulsory restraint intervention while controlling for cycles and other long-term patterns in each injury time series. All percentage change esti-

| for Motor Vel | s by Body Region hicle-Related lizations |
|------------------------|--|
| Injured Body Region | No. (%) |
| Head | 3146 (34.7) |
| Neck | 594 (6.5) |
| Back/spine | 455 (5.0) |
| Thorax | 879 (9.7) |
| Abdomen | 504 (5.6) |
| Extremities | 2717 (30.0) |
| Other | 775 (8.6) |
| Total | 9070 (100.1)* |

*Total percentage is greater than 100 due to rounding.

mates reported herein are based on such intervention models and represent statistically significant changes in injury rates associated with the restraint law from the level expected, had the law not been implemented.

Because the models are intrinsically nonlinear, the Gauss-Marquardt method implemented in the computer program BMDP 2T was used to estimate the parameters. ^{15,16} Each model was carefully evaluated in terms of the multiple criteria suggested by Box and Jenkins. ¹⁴ When inadequacies were found, the model was respecified, reestimated, and reevaluated until a parsimonious model was obtained that adequately accounted for all of the significant autocorrelation patterns in the original series.

Several features of this type of intervention preclude the simple comparison of means before and after the laws or the use of ordinary least squares regression. First, the primary dependent or outcome variable is the monthly injury rate. In a clinical study of the outcome of an intervention or treatment, the individual cases are assumed to be statistically independent, an assumption that allows the investigator to apply equal weights to each case in the generation of means. In contrast, the "cases" under study here are monthly rates that are clearly not independent. The rate in a given month is correlated with the rate in preceding or following months. The monthly rate immediately preceding an intervention is more closely correlated with the subsequent rate than a monthly rate that is farther removed. A simple comparison of the mean of the monthly rates for the 27 months before the intervention with the mean for the 45 months following the intervention assumes that each rate is completely independent of the rates in all other months. Second, ideally individuals would be randomly assigned to treatment or intervention groups. Since in the case of the implementation of a law, however, this obviously cannot be done, it is necessary to evaluate the intervention by using a

| Injury Rate | Adjusted R ² | Estimate* | Change, % |
|----------------------------|-------------------------|-----------|-----------|
| Head injuries | | | The Table |
| Crude | 0.210 | -0.5141 | -40.2 |
| Per population | 0.377 | -0.1831 | -16.7 |
| Per vehicle miles traveled | 0.425 | -0.2171 | -19.6 |
| Per No. of crashes | 0.520 | -0.2842 | -24.7 |
| Extremity injuries | | | |
| Crude | 0.449 | -0.5224 | -40.7 |
| Per population | 0.511 | -0.1541 | -14.3 |
| Per vehicle miles traveled | 0.539 | -0.1670 | -15.4 |
| Per No. of crashes | 0.506 | -0.2182 | -19.6 |
| All injuries combined | | | |
| Crude | 0.326 | -0.7006 | -50.4 |
| Per population | 0.454 | -0.3175 | -27.2 |
| Per vehicle miles traveled | 0.487 | -0.3634 | -30.5 |
| Per No. of crashes | 0.518 | -0.4440 | -35.9 |

^{*}All estimates are significant at P<.05.

quasi-experimental rather than randomized experimental design. 17

Box-Jenkins interrupted time-series analysis is essentially a variation on ordinary least squares regression that takes into account the lack of independence among data points, or more specifically the serial or autocorrelation among error terms. 12 This analytic technique allows the calculation of a parameter estimate that is analogous to a B weight in regression. The equations permit the measurement of the discontinuity in the trend line at the time of the intervention, which is entered into the analysis in the form of a dummy variable. Data are log transformed to reduce the degree to which the variance of the dependent variable changes over time (ie, reduce their heteroscedasticity). In other words, the technique permits a calculation of the size and statistical significance of the discontinuity associated with the intervention and allows one to state that the monthly rate is now a calculated percentage different than would have been expected had there been no intervention.

RESULTS

The 16 hospitals that regularly use E codes reported a mean of 1512 discharges per year (range, 1444 to 1653) related to passengers in motor vehicles, for a total of 9070 from 1980 through 1985. Table 1 contains the frequency distribution of injuries in the entire sample of passengers and shows that the distribution is comparable with other investigations of motor vehicle passenger injuries. ¹⁷ Of the total of 9070 cases, 187 discharges (2.1%) were of children aged 4 years or younger.

Figure 1 shows the monthly rates of hospitalization for the period under study. As indicated in Table 2, the crude rate of hospitalization for all injuries following the implementation of the restraint law is 50.4% lower than the rate expected had pre-1982 trends continued. Rates for head and extremity injuries were 40% lower than expected.

Since Fig 2 shows a decline in the population of children younger than 4 years and an increase in both miles traveled and crashes, the hospitalization rates were adjusted for those factors. Table 2 indicates that the rate for head injuries declined for all three types of adjustment, per population (-16.7%), per vehicle miles traveled (-19.5%), and per vehicle crashes (-24.7%). Not surprisingly, both before and after implementation, head injuries accounted for the largest proportion of injuries requiring hospitalization. The increase in the proportion of all injuries that were head injuries (even though the rate decreased) suggests that other injuries have declined substantially. As shown in Table 2, extremity injuries declined, with the largest decline manifest when adjusted for crashes (-19.6%). Although the frequencies of injuries to the neck, back, abdomen, and thorax were too low to reveal statistically significant changes, the rate for all injuries combined declined by 35.9% when adjusted for vehicle crashes.

Although no direct measure of in-

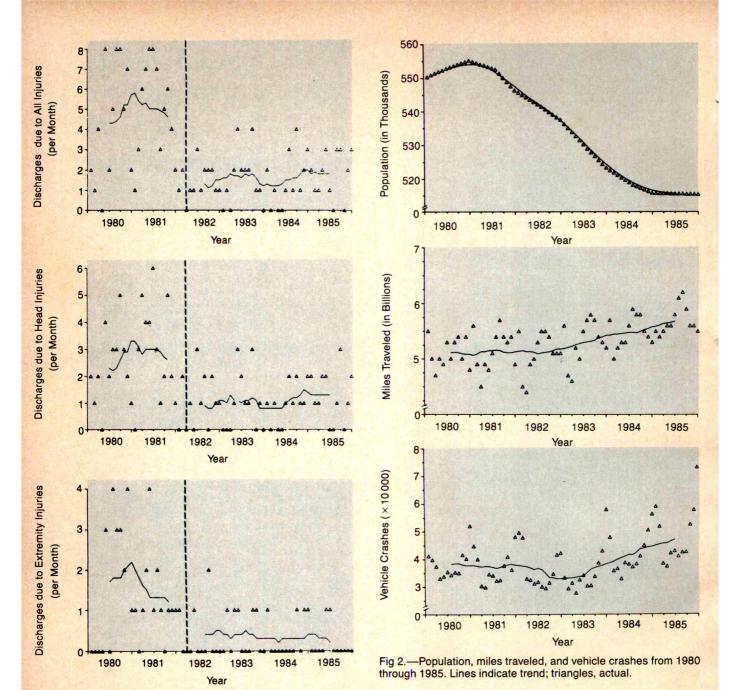


Fig 1.—Total, head, and extremity injury discharges before and after April 1982. Triangles indicate monthly number of discharges; lines, 12-month moving average. There is discontinuity in trend line for six-month periods before and after intervention to exclude April 1982 intervention from moving average.

jury severity is available in the database, length of stay has been used as a proxy. We trichotomized length of stay into short (under two days), medium (greater than two but no more than seven days), and long (more than seven days). The rate of injured occupants requiring a short length of stay declined by 48% and the rate of hos-

pitalization requiring a long length of stay declined by 25.5%. Time-series model estimates indicated the rate of hospitalizations requiring a medium length of stay declined by 17.6%, but the 95% confidence interval included 0. An alternative explanation for the decline in length of stay is that economic and insurance pressures have

encouraged shorter hospital stays, but that long-standing slightly downward trend in Michigan fails to account for the pronounced decline we found beginning in the exact month the child restraint law was implemented. Specifically, unpublished MIDB data indicate that between 1980 and 1985 the mean length of stay for pediatric admissions declined by slightly greater than 4%.

COMMENT

This study demonstrates that implementation of a child restraint law and the subsequent increase in restraint use is associated with substantial declines in at least two clinical entities—head and extremity injuries. Furthermore, severity of motor vehicle—related injuries, as reflected in length of hospitalization, has decreased. Documentation of these declines in frequency and severity of injuries is particularly valuable since infrequent deaths limit the ability to demonstrate declines in mortality following this type of intervention. 18

It is important to note that when no adjustment was made for level of exposure, the change in the trend from before to after the law's implementation was the most impressive. The failure to adjust for changes in population, mileage, and crashes is potentially misleading, however. For example, a large increase in mileage or population could increase the number of hospitalizations, leading to the inaccurate conclusion that the law had been ineffective. Given the need to adjust, conclusions about the effectiveness of the law are strengthened

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by the fact that the most rigorous adjustment (for number of crashes) produced the largest declines for each outcome measured. The disparate rates emphasize the importance of determining rates that are based on exposure to driving in general, and crashes in particular.

Intervention analysis using timeseries techniques provides the capability to assess accurately the effects of community interventions. When longitudinal data are available, these techniques permit analysis though the monthly rates themselves are low, and randomization into intervention and nonintervention groups is not possible. The availability of this technique is particularly valuable to demonstrate effectiveness for legislators and other policymakers who are ultimately responsible for the implementation and continuation of legislation such as a mandatory child restraint law

Computerized inpatient databases offer the opportunity to monitor the effects of legislation such as the mandatory child restraint laws. 19 Unfortunately, since financial management is the major motivation for the collection and maintenance of hospital data, health-related data are not recorded as accurately and completely as pos-

sible. For example, E codes are central to the assessment of injuries and to the formulation of strategies to decrease their rates. Because the external cause of injuries is perceived as having little bearing on hospital functioning or needs, E codes are not regularly recorded.

Emerging studies demonstrating the clinical effectiveness of restraint systems for children represent an important step in the recognition of and intervention for this major child health problem. Beginning with laboratory studies, motor vehicle passenger safety has progressed through the stages of public information, legislation for mandatory use, and recognition of the effectiveness of child restraints in large clinical field trials. This sequence points toward two new challenges in the field of passenger safety: (1) increasing the proportion of children who use restraints from the current levels of approximately 60% to 70%, and (2) recognizing and promoting the correct use of restraints.20

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Educational Interventions

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Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—Is there a national uniform view of combined internal medicine-pediatrics training programs by the various medical directors of these programs? How do these programs differ from family practice training? What is the attrition rate within these programs? In this article, Siegel et al address many of these issues. See where your combined program fits into this spectrum of opinion given us by the various directors of such programs.—H.D.A.

Demographic Features and Attitudes of Program Directors of Combined Internal Medicine and Pediatrics Residencies

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◆ Combined residency training in internal medicine and pediatrics has proliferated greatly in the last ten years. This survey of program directors (N = 55) of such residency programs reports their personal and professional demographic characteristics as well as their perceptions about aspects of combined training. The directors were more often affiliated with internal medicine (33 directors [60%]), 47 (85%) were men, their mean age was 44 years, they had been out of medical school for a mean of 19 years, the mean time served as program director was 2.6 years, and 32 (58%) had

In the last ten years there has been a marked proliferation in residency programs that offer combined training in internal medicine and pediatrics. The 1980 National Residency Matching Program listed four programs that completed a fellowship. The programs had existed for an average of 4.2 years, the mean entering class size was 2.8 persons, and the mean number of graduates per program was 4.2. We report directors' perceptions of why students choose combined training, why the programs have proliferated, and how these residents differ from family medicine residents. We comment on curriculum design and the goals of combined internal medicine—pediatrics residency training programs.

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offered nine total positions for combined internal medicine and pediatrics residents, while the 1987 National Residency Matching Program listed 70 such programs offering a total of 206 training positions. Parallel to the growth in the number of programs, there has been increased discussion regarding the ideal training curriculum. Program directors, the American Board of Pediatrics, and the American Board of Internal Medicine are all actively involved in assessing the training and performance of internal medicine and pediatrics physicians. Unfortunately, there is no national data bank available on these trainees or graduates. We must rely on individual surveys of these program directors and graduates to better characterize this newly emerging breed of physician.

To our knowledge, only four articles specifically devoted to combined training in internal medicine and pediatrics have been published. The history of combined training is described by Peterson and Goldenberg, and two curriculum surveys1,2 have recently been published. The outpatient curriculum at one training program is detailed in another article.3 Finally, Greganti and Schuster described the experience of the University of North Carolina, Chapel Hill, and the University of Rochester, NY, and they specifically noted the problem of high attrition rates for internal medicine and pediatrics trainees.

We present herein the results of a survey of internal medicine and pediatrics program directors conducted in 1987 that focuses on descriptive features of the training programs and directors and explores director perceptions regarding motivations for the

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trainees as well as perceived needs and goals.

METHODS

We developed a survey questionnaire consisting of 18 items, including the following: (1) personal demographic characteristics of the directors (age, gender, year of graduation from medical school, number of years as director of the combined residency program, and whether the individual had pursued fellowship training), (2) size and history of the combined residency program (number of residents accepted into each first-year group, total number of residents in the four-year program, how many years the program had existed, and how many residents had graduated from the program with training in both specialties), and (3) the attitudes of the director concerning such issues as why students choose combined training, why these programs have proliferated in the last several years, whether strong primary-care training programs should be in place at an institution where combined training is offered, and how internal medicine and pediatrics graduates differ from family medicine graduates.

The population surveyed was selected through a multistep procedure. The 1986-1987 Directory of Residency Training Programs⁵ was consulted for the list of 81 programs described in an appendix as offering combined residency training in internal medicine and pediatrics. Someone at each of these programs was then contacted by telephone to ascertain whether the program was active (currently offering firstyear residency positions to graduating medical students who plan to complete a four-year combined residency), who was directing it, and other information concerning the number of residents-in-training, the number of graduates, etc. Based on this preliminary work, the survey instrument was sent to the directors of active programs, followed by a second mailing to initial nonresponders. A cover letter accompanying the questionnaire explained the purpose of the study and asked that the person or persons directing the combined residency program respond to the questions even if this was not the individual to whom the questionnaire was initially mailed. Despite the directory listing and our telephone contact, it remained unclear in some instances who was actually directing the program. Of the 81 programs listed in the directory, 70 were active, and we received responses from 55, for a response rate of 79%. If codirectors returned questionnaires, the quantifiable data were averaged and counted as one response.

In the data analysis we sought to determine the attrition rate of residents in the combined programs by calculating a theo-

retical "ideal" number of graduates for each program that had existed long enough to graduate residents. The following formula was used to determine the percentage of residents who completed training in both specialties:

No. of Actual Graduates
(No. of First-Year Residents) ×
(No. of Years Program Has Existed -4)

RESULTS

As shown in Table 1, the mean age of the directors was 44 years; 47 (85%) were men, and eight (15%) were women. The mean number of years since graduation from medical school was 19. The department of primary appointment was more often internal medicine (33 directors [60%]), over half (32 [58%]) of the directors had undergone fellowship training, and the mean time spent as director of the combined residency program was 2.6 years. Twelve respondents were also directors of the traditional internal medicine or pediatrics residency training program and had been directors for longer than the combined program had existed in their institutions. However, only the years as director of a combined program were counted.

The national distribution of the residency programs showed an eastern and midwestern predominance, with 38 programs (69%) located in the following states: Michigan (eight), Ohio (seven), New York (six), Illinois (five). New Jersey (four), West Virginia (three), Pennsylvania (two), Massachusetts (one), Connecticut (one), and Indiana (one). Nine programs were located in the West: Texas (four), California (three), Arizona (one), and Oklahoma (one); one each of the remaining eight programs was located in states in the southeast and the Mississippi Valley.

Characteristics of the residency programs are summarized in Table 2. A mean of 2.8 residents per program were accepted in first-year positions; the mean total number of residents enrolled was 7.4 per program. In calculating the number of residents who had graduated we only looked at the 31 programs that had existed for four or more years; there was a mean of 4.2 graduates per program. While the mean age of the programs was found to be 4.2 years, the distribution was not normal, and, in fact, two thirds of

Table 1.—Characteristics of 55 Combined Internal Medicine and Pediatrics Residency Program Directors in 1987

| Characteristic | Responses |
|---------------------------|-----------|
| Discipline, No. (%) | |
| of directors | |
| Internal medicine | 33 (60) |
| Pediatrics | 22 (40) |
| Sex, No. (%) of directors | |
| M | 47 (85) |
| F | 8 (15) |
| Age, y | |
| Mean | 44 |
| Range | 29-65 |
| Time since graduation fro | m |
| medical school, y | |
| Mean | 19 |
| Range | 5-45 |
| Fellowship training, | |
| No. (%) of directors | |
| Yes | 32 (58) |
| No | 23 (42) |
| Time as program | |
| director, y | |
| Mean | 2.6 |
| Range | 1-6 |

Table 2.—Characteristics of 55 Combined Internal Medicine and Pediatrics Residency Training Programs in 1987

| Characteristic | Responses |
|-------------------------|-----------|
| Age of program, y | |
| Mean ± SD | 4.2 ± 3.3 |
| Range | 1-16 |
| No. of persons entering | |
| programs | |
| Total | 151 |
| Mean | 2.8 ± 1.3 |
| Range | 1-6 |
| No. of persons enrolled | |
| in programs | |
| Total | 408 |
| Mean | 7.4±5.2 |
| Range | 1-23 |
| No. of graduates* | |
| Total | 130 |
| Mean | 4.2 ± 4.9 |
| Range | 0-18 |

*For the 31 programs that had existed for four years or more.

the programs had been active for only four or fewer years.

In exploring the problem of attrition among residents we used the formula described in the "Methods" section and found a mean dual specialty completion rate of 69%, with a range of 0% to 250%. There are two sources of error in this calculation. One is that the number of residents accepted into the first year has not always remained constant throughout the life of a program. Thus, the denominator could actually be greater than calculated in the formula. This error biases toward

Table 3.—Reasons Given by Residency Program Directors for Why Medical Students Choose Combined Internal Medicine and Pediatrics Residency

| Reason | No. of Responses |
|------------------------------|---------------------|
| Preferred alternative to | |
| family medicine | 31 |
| More in-depth training | 23 |
| Desire to care for | |
| patients of all ages | 22 |
| Primary-care orientation | 14 |
| Undecided between internal | |
| medicine and pediatrics | 9 |
| Subspecialty preparation | 5 |
| Desire for a broad education | 2 |

a higher calculated completion rate than might actually be the case. In addition, some programs accept transfers into the last three years, resulting in a higher number of actual graduates. This increases the numerator and again biases toward a higher calculated completion rate. These potential errors explain why the range is greater than 100%. The calculated dual specialty completion rate of 69% is therefore probably somewhat overstated.

A variety of responses were given in answer to the question "Why do medical students choose internal medicine and pediatrics residency training?" (Table 3). Most directors listed several reasons, and all were counted. According to the program directors, the most common reason students chose combined training was as a preferred alternative to family medicine training. This was followed in rank order by a desire for in-depth training and the goal to care for patients of all ages. Less common responses were that the students were oriented to primary care, undecided as to which specialty to pursue, in search of subspecialty preparation, or looking for a broad education.

In a related question the directors were asked "Why has there been such a proliferation of internal medicine and pediatrics programs in the last several years?" By far the most common response was that this training is an alternative to family medicine training (Table 4). Many responses were sharply critical of family medicine training. Other reasons included the realization that many family physicians do not practice obstetrics and

Table 4.—Reasons Given by Residency Program Directors for the Proliferation of Combined Internal Medicine and Pediatrics Residencies

| Market Market Control | Reason | | No. of Responses |
|--|------------------------|----------------|--|
| | | | 33 |
| Alternative to family medici | | | 그는 사람들은 아이들은 사람들은 사람들이 되었다면 하는데 살아 있다. |
| Increased medical student | | | 16 |
| Family physicians end up n once in practice | ot performing obstetr | ics or surgery | 12 |
| Attracts better residents the | an traditional program | s | 6 |
| Less demand for subspecia | alty training | | 2 |
| Better personal income for | graduates | | 2 |
| Better pediatric training | • | | 2 |
| "Poor counseling" by media | cal school deans and | | |
| department chairmen in | | • | |
| to seek combined trainin | | | |
| Easily fits into already esta | | | |
| training (internal medicin | | | 1 |

Table 5.—How Residency Program Directors Think Combined Internal Medicine and Pediatrics Residency Graduates Differ From Family Medicine Residency Graduates

| Difference | No. of Responses |
|--|---------------------|
| Greater depth of training | 40 |
| Better inpatient skills | 12 |
| Greater potential for an academic career | 11 |
| Not trained in obstetrics or surgery | 11 |
| Better integration of basic and clinical sciences | 7 |
| Internal medicine and pediatrics graduates see themselves as specialists | 7 |
| Better critical care skills | 6 |
| Better pediatric skills | 5 |
| Fewer outpatient skills | 4 |
| Less difficulty in obtaining admitting privileges | 3 |
| Less interest in psychological issues | 3 |
| Better outpatient skills | 2 |

surgery, making it impractical to undertake training in primary-care programs that include these areas. Some directors believe that the combined program attracts better-quality residents than the traditional internal medicine or pediatrics programs alone. One director believed combined training is a bad idea and considers it "poor counseling" by deans and chairmen to encourage medical students to request this training.

Because we anticipated the comparison with family medicine, we asked directors how internal medicine and pediatrics graduates differ from family medicine graduates. The respondents most frequently listed greater depth of training as an advantage for internal medicine and pediatrics graduates, followed in frequency of response by better inpatient skills and greater potential for an academic career (Table 5). Interestingly, different directors believed that the outpatient skills of internal medicine and pediatrics graduates were both worse and better than those of family medicine graduates.

The question often arises whether graduates of combined programs are adequately prepared to achieve board certification in both specialties. Of the 53 directors who responded to this question, 47 (89%) stated that graduates are adequately prepared, but six directors (11%) disagreed. One must be concerned about programs in which the director doubts the ability of graduates to attain appropriate credentials. When asked to estimate the percentage of residents who would complete four years of training, 48 (87%) of the respondents wrote that between 65% and 70% of residents would complete the training. This is in agreement with the calculated theoretical finding of 69% reported earlier.

Directors were asked to comment on the importance of having strong primary-care programs in internal medicine and in pediatrics in an institution before setting up a combined residency. Although combined residencies have been labeled as primarycare training⁶ and previous reports have described such an emphasis,¹ a survey of graduates from two programs showed that almost half of these physicians were in non-primary-care careers. An almost equal number of directors vehemently agreed and disagreed that a strong primary-care training curriculum is essential to a combined residency program (28 said that a primary-care curriculum is important, 24 said it is not).

Directors were asked if they thought specific curriculum guidelines should be established for combined residencies. Most (39 [71%]) believed that guidelines should be established, but about one fourth of the directors (14) considered such guidelines to be restrictive and said that programs should be free to establish their own curricula.

COMMENT

With the dramatic increase in the number of internal medicine and pediatrics combined residency training programs, information about curriculum design and program directors is important to understand the sort of training residents are receiving. The directors in our survey are comparable in age and gender to a group of internal medicine program directors surveyed in 1982,7 although that study used a slightly older (mean age, 49 years) and more male (98%) group of directors who had been in their positions about twice as long (mean, five years) as the directors in our survey. To our knowledge, a similar survey of program directors in pediatrics has not been reported.

Although directors have reached a consensus that combined residencies have a role as an alternative to family medicine training, this is not supported by their positions concerning primary-care training in internal medicine and pediatrics residencies. The goal of family medicine residencies is to prepare physicians to provide family-centered primary care. Almost one half of the internal medicine and pediatrics residency program directors stated clearly, however, that strong primary-care training is not a necessary part of a combined residency program. Obviously, the programs with these directors are not likely to put a heavy emphasis on primary care. Thus, combined training programs in internal medicine and pediatrics cannot be assumed to be a real alternative

to family medicine programs for preparing primary-care physicians, although some programs do have a commitment to primary care.

In accepting this conclusion, one must take into account that we did not define primary care in the survey instrument. Program directors may perceive this descriptive term to have different meanings, but the majority of responses included a discussion of the role of primary care in postgraduate training, suggesting that the directors shared a similar understanding of primary care. We believe the term has been used and defined commonly enough in a variety of contexts (journal articles, professional society names, federal residency training grant applications) so that the questionnaire item concerning the importance of primary-care training in combined residencies was valid.

The career choices made by the groups of graduates surveyed to date do not show a predominance of primary-care positions. Greganti and Schuster found, however, that the University of Rochester program represented most of the graduates oriented to primary care, while the University of North Carolina graduated most of the subspecialty-oriented physicians. We are undertaking a study of graduates from combined residency programs nationwide to better understand the career choices made by these physicians and their opinions concerning combined residency curricula.

The role of internal medicine and pediatrics training in the preparation of primary-care physicians is a timely issue. A group of articles published in 1986 reiterated the desperate need for primary-care physicians in the United States and proposed various training alternatives to meet the demand.8-11 Geyman⁸ pointed out that a previous national goal for 50% of all physicians to enter primary-care specialties was in fact too low, and medical educators should be preparing 70% of all physicians to be involved in primary care. In contrast to this projected need. currently, only about 30% of medical school graduates are entering primary-care specialties, and by the 1990s, only about 40% of all physicians in the nation will be in primary care.8

One response to this problem was presented by Christiansen et al⁹ and

involves the establishment of combined family practice and internal medicine residencies. The proposal points out the great overlap between the primary-care training offered in family practice and internal medicine residencies and suggests assimilation of their respective strengths into a single four-year program. The authors recommend that the training prepare graduates for both board examinations, with the possibility that a new certification board (for this new primary-care physician) will be developed. The American Board of Internal Medicine and the American Board of Family Practice have continued to discuss this experiment, but a formal collaboration has yet to emerge. The recent establishment of certification in geriatric medicine jointly sponsored by both boards sets a precedent for constructive cooperation, but the creation of a new four-year residency program is certainly a much more ambitious undertaking.

While Colwill¹⁰ and Friedman¹¹ provided editorial responses to these articles, a major topic left virtually unaddressed by all of these authors is that of pediatrics. In fact, despite much discussion of the need for and the means by which to prepare the most effective primary-care physician, the word pediatrics literally appears but once in the whole of the article by Christiansen et al.⁹ These articles share a similar paucity of comment concerning child health care.

Training in pediatrics is certainly a part of family practice residencies, but most programs rely on pediatrics residencies to provide that portion of family practice education. So much of child health care is provided in primary-care settings that any complete primary-care physician must be well grounded in skills in pediatrics. A thorough understanding of the unique physical and developmental aspects of children is essential to provide comprehensive family-centered care. This background in pediatrics is already a required part of family practice training, but the formal organizations that represent graduate medical education in pediatrics must play a central role in developing any new primary-care training pathways.

Is combined internal medicine and pediatrics training the answer to this question of the ultimate primary-care residency? Ferrari⁶ argued that it is, and one might assume that such a residency combination prepares graduates for primary care. Our survey reveals, however, that directors do not unanimously see their programs as serving that purpose. Directors are not the only predictors of the emphasis of training programs, but they set the tone and direction for residents by being role models and by curriculum design. Those who favor a primarycare mission for internal medicine and pediatrics residencies need to accomplish a standardization of curriculum and attitude among the programs before these combined residencies can be seen as the prototype for a generic primary-care residency. We believe that equal participation by family practice leadership is necessary in restructuring current internal medicine and pediatrics programs if they are to provide the comprehensive behavioral and family systems training necessary to produce a truly ideal primary-care physician.

Also of concern is the ambivalence on the part of some directors regarding the credibility of combined training. Though discussion of the challenge of taking on two specialties deserves attention, directors of combined programs should have already concluded that such training is valid and should communicate this sentiment to their trainees. We found in our survey that six directors doubted the ability of their graduates to achieve certification in the two specialties in which they were training. Moreover, one director believed that students were being improperly counseled in being encouraged to apply to such programs. Perhaps the directors were questioning the appropriateness of the respective certification boards as a means of testing the qualifications of internal medicine and pediatrics graduates rather than doubting the abilities of the residents. We are concerned, however, that these directors may not represent the sorts of role models likely to be constructive and supportive in working with internal medicine and pediatrics residents.

Finally, the problem of attrition was profound. Programs appeared to be graduating only about two thirds of the residents who began the four-year residency, according to our theoretical completion rate. This is a collective figure that is undoubtedly inaccurate for many individual programs. Though we were unable to gather reliable actual data concerning completion rates (this information was requested in the initial telephone survey), data presented recently revealed a reported (by programs) completion rate of 65% and suggested that of these who did not complete the four-year program, 40% went on to finish in pediatrics alone and 30% in internal medicine alone.12 The fate of the remaining 30% was not reported. Friedman and Rolfe18 reported an attrition rate of a little over one third (using actual data from programs), with 34% of this group entering pediatries and 37% entering internal medicine. Our calculated rate is consistent with these actual rates, though this descriptive statistic applies only to the programs as a group.

Is combined training too overwhelming, resulting in this high dropout rate, or are medical school candidates not well screened for those who are not decided between the two specialties and really do not intend to finish in both? Scheduling in residencies is usually quite rigid, and unexpected departures of residents place considerable stress on the system, including the other residents. This is particularly true in internal medicine

and pediatrics training, in which many programs pair residents to meet coverage needs in both internal medicine and pediatrics services. Thus, attrition affects not only the credibility of combined training but also the staffing of hospital residency positions.

There is no doubt about the popularity and proliferation of combined internal medicine and pediatrics residency training programs in recent years, and reports have begun to appear describing the structure of such programs. 1,2 This survey described a group of middle-aged, predominantly male program directors, almost two thirds of whom had fellowship training, among whom there was a large variance of opinion as to the purpose and goals of combined training. Further research into the graduates of such programs is needed, but programs can have very different emphases, and students must choose a site of training based on their own career goals (primary care vs specialization) and how well a given program's (and its director's) philosophy matches a student's training needs. We recommend that directors of combined residency programs make known to medical student candidates the areas of emphasis within their programs so that candidates and residencies can rank their choices accordingly. We are currently involved in surveying the graduates of combined residency programs nationwide to gather their perspectives on the strengths and weaknesses of their respective residency experiences. Observations by directors and graduates will provide important background information for designing optimal combined internal medicine and pediatrics residencies.

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Rehospitalization of Very-Low-Birth-Weight Infants

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 Very-low-birth-weight (VLBW) infants are at high risk of mortality, morbidity, and rehospitalization in the first years of life, but little information is available to predict which VLBW infants are likely to require rehospitalization. This study describes a sample of 79 VLBW infants cared for in a charity hospital. The sample was predominantly black, and the majority of the mothers were young and unmarried. Some of the infants were followed up by a multidisciplinary High-Risk Follow-up Clinic, and all were tracked until their second birthdays to determine the rate of rehospitalization. Using multiple regression, we present herein a model that accounts for 51% of the variance in rehospitalization; the model includes mother's age, education, and marital status: infant birth weight and gestational age; the use of prenatal care and the High-Risk Follow-up Clinic; and three quadratic terms. Although the significance of the quadratic factors in the model makes explanation of these results difficult. results suggest that the model can be used to predict whether infants will require rehospitalization in the first two years of life.

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Infants born at weights of less than 1500 g, ie, very-low-birth-weight (VLBW) infants, are at grave risk of mortality and morbidity. Despite marked improvements due to neonatal intensive care (NICU) technology, such infants are more likely than infants of normal birth weight to die during the first month of life, and survivors continue to be more likely

to die throughout the first year of life.

Surviving VLBW infants also have higher rates of morbidity in the first years of life than their normal peers, particularly from respiratory infections. ^{2,3} It is thus not surprising that McCormick and colleagues found that 38.2% of VLBW infants were rehospitalized in the first year of life, compared with 9.1% of normal-birthweight infants.

Mutch et al's review⁵ of research on rehospitalization of VLBW infants demonstrated an increase during the period from the 1940s to the 1980s in the relative risk of rehospitalization for VLBW infants compared with various comparison groups. For example, studies published in 1976,4 in 1977,6 and from 1980 to 19827 show one-year readmission rates ranging from 33.0% to 53.0%. Results varied among followup studies due in part to the conditions used to select the study sample (many studies eliminated infants with congenital malformations, for example) and the length of the follow-up period. Despite the variation, however, it is certain that the increasing capability of NICU technology to save smaller and more immature infants results in increasing numbers of fragile infants surviving to discharge and thus being at risk for morbidity and hospital readmission.

Previous studies have described the risk of rehospitalization to increase as birth weight decreases,⁴ as might be expected. Efforts to predict rehospitalization among a population of low-birth-weight (<2500 g) infants have found relationships between return to the hospital and low income,⁸ receipt of public assistance,⁹ and young maternal age.^{19,11}

Young maternal age, which is highly correlated with low birth weight, also is associated with failure to obtain proper prenatal care, receipt of public assistance, and the absence of a father in the home, all of which were related to rehospitalization in the first nine months of life in the study by Glass et al. McCormick et als found that during the first year of life, rates of rehospitalization for low-birth-weight infants ranged from only 7% for infants of affluent families to 20% for infants from disadvantaged families.

Low maternal education and unmarried status, which are highly correlated with low income and young maternal age, place low-birth-weight infants at excess risk of mortality, 2 so these variables also would be expected to increase the risk of morbidity and rehospitalization. This increased risk might be due to a lack of knowledge regarding the appropriate use of preventive and primary health care resources, inadequate social support and nutrition, and other factors among younger, poorer families.

The ability to predict rehospitalization among VLBW infants would be advantageous because it might enhance follow-up and provision of adequate services to those at greatest risk, thus possibly preventing rehospitalization. With increasing calls to reduce the staggering cost of medical care, and especially that portion borne by the public, such information might allow limited resources to be directed toward those with the most need. Less time spent in the hospital due to illness also might promote the more normal healthy development of high-risk infants

SUBJECTS AND METHODS Subjects

The study population included 95 infants (and their 90 mothers) whose birth weights were equal to or less than 1500 g; who were born between Jan 1, 1982, and Dec 31, 1983; and who survived to discharge from the NICU of Earl K. Long Memorial Hos-

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Reprint requests to School of Social Work and Community Planning, University of Maryland, Baltimore, MD 21201 (Dr Combs-Orme). pital (EKL), which is part of the Louisiana Charity Hospital System. Infants who were born in the hospital (N=90), those who were transported to this regional perinatal center from other hospitals (n=2), and those brought to EKL following birth outside a hospital (n=3) were included.

Data Collection Procedures

After approval by the Human Subjects Committee, two types of data were collected from the infants' medical records. First, basic social data including data about sociodemographics and family composition (at the time of the infants' birth) for the surviving 95 infants were collected where available by four advanced social work students under the supervision of one of us (T.C.-O.). The students also recorded data about pregnancy history from birth certificates (found in the medical records), medical utilization data (hospitalizations, emergency room visits, and High-Risk Follow-up Clinic [HRFC] appointments) from the medical records, and information about circumstances and causes of death from death certificates found in the records.

Second, extensive medical data (including diagnoses, laboratory results, and medications) from the birth and nursery course were abstracted by a neonatologist (J.F.), Data about the HRFC visits (including diagnoses, screening and testing results, and community referrals) were recorded by a neonatal nurse (C.S.). The data of randomly selected cases were compared with the original records by one of us (T.C.-O.) and the neonatal nurse to check for accuracy. Additional data were obtained from the local Chief Coroner's office for infants who died during follow-up; from other hospitals, clinics, and social agencies where some infants received services; and, in a small number of cases in which there were discrepancies on certain variables, from the mothers. (This was necessary in rare cases in which the records were unclear.)

Setting

A two-year follow-up of these infants was possible because all NICU survivors at EKL are automatically enrolled in the HRFC before hospital discharge and aggressively followed up. Regular appointments are scheduled, the frequency depending on the age and condition of the child and the identified environmental risk factors, such as a substance-abusing parent. The HRFC staff consists of an attending neonatologist, pediatric residents, a high-risk follow-up nurse, social workers, educational consultants provided by the local school system, speech therapists, audiologists, and physical therapists.

Failure to keep HRFC appointments results first in a letter, then a second letter, and then referral to a public health nurse or child protection agency, depending on the nature of the child's condition. Identification of nonmedical problems such as significant developmental delay or hearing impairment results in referral to appropriate community agencies such as the Early Intervention Program or the Speech and Hearing Foundation. Close communication is maintained by the HRFC personnel with the community agencies and the parents to ensure coordination of services and consistency of care. Similar follow-up clinic procedures were described by Glass et al.9

Statistical Analysis

Hierarchical multiple regression was used to test a model constructed on theoretical grounds to predict rehospitalization, using those variables that are most often available through medical records. Several cases were excluded to accommodate the needs of the statistical procedure. First, infants who died (n=6) during follow-up were excluded because their period of risk was truncated, and the statistical method could not accommodate this truncation. Second, to preserve the independence of subjects, one case in each set of twins (n=4) and in the one set of siblings was randomly excluded from the analysis. Finally, cases with missing data (5.6%) reduced the sample available for analysis to 79. The results of the study thus should be taken with some caution, since a sample of this size may limit the precision of the obtained estimates.

In the hierarchical procedure, blocks of predictors are entered one by one (in logical order according to availability of the data to a clinician) to facilitate an incremental evaluation of the model at each point. As each block of variables is entered, statistics indicate whether the addition of those variables significantly improves the ability to predict rehospitalization over and above the predictive ability of the previous model. In addition, the adjusted R^2 value indicates what proportion of the variance in rehospitalization is accounted for by the model, that is, how much of the variation among cases in the number of rehospitalizations can be explained by the model. In these analyses the adjusted R^2 value is used to produce a conservative figure corrected for chance and sampling variation. Diagnostic statistics may be used to test the assumptions of multiple regression, which may threaten the validity of results if they are not met.

Data analysis was performed using the regression procedure of the SPSS/PC Plus software package. 13

| Table 1.—De | scription of the (N = 79) | iption of the Sample i = 79) | | | | |
|---|----------------------------|---------------------------------------|--|--|--|--|
| Variables | Mean (SD) or Proportion | Range | | | | |
| Race/sex, % B/M | 32.9 | | | | | |
| B/F | 49.4 | | | | | |
| W/M | 5.1 | | | | | |
| W/F | 12.7 | | | | | |
| Birth weight, g | 1233.4 (213.6) | 660-1500 | | | | |
| Gestational age, wk | 31.8 (2.2) | 27-39 | | | | |
| Maternal age, y | 22.1 (5.1) | 14-35 | | | | |
| Maternal education, y | 11.6 (1.7) | 7-17 | | | | |
| Mother unmarried, % | 67.1 | ••• | | | | |
| Prenatal care, % Began first trimester | 59.6 | · · · · · · · · · · · · · · · · · · · | | | | |
| <5 visits | 65.8 | • • • | | | | |

RESULTS

Table 1 describes the sample. Sixty-four (81.0%) of 79 infants were singletons, 14 (17.8%) were twins, and one (1.2%) was a triplet. As Table 1 shows, 82.3% of the infants were black, 67.1% of the mothers were unmarried, and 41.8% had less than a high school education. All infants were followed up from birth to their second birth-days (age not corrected for gestation).

Table 2 demonstrates that this was a very-high-risk sample of infants. Over one third (36.7%) were small for gestational age. Four infants had significant congenital malformations at birth. Most suffered from respiratory distress syndrome and required mechanical ventilatory assistance. The infants were hospitalized (including the time spent at other hospitals to which they were transferred, and time in both the NICU and Progressive Nursery where they were transferred on stabilization) at birth for a mean of 53.5 (SD, 27.9) days (range, ten to 170 days).

Table 2 also shows the two-year outcomes for this sample. About one third of the infants were rehospitalized at least once during the follow-up period. In addition, six infants were not included in the analyses because they died following discharge or during the

| Table 2.—Birth and Folk | w-uj | Data |
|--|--------|----------|
| Variables | ٧ | alues |
| No. of days in hospital at birth Mean (SD) | | 5 (27.9) |
| Range | 1 | 0-170 |
| Small for gestational age, % | 36. | 7 |
| Delivery by cesarean section, % | 38.6 |) |
| Birth complications, % None | 35.4 | 4 |
| Placenta previa with abruption | 16. | 5 |
| Prolonged rupture of membranes | 21.6 | 5 |
| Preeclampsia | 16.5 | 5 |
| Maternal infection | 5. | ı |
| Other | 3.9 | • |
| No. (%) of rehospitalizations None | 54 | (68.4) |
| 1-2 | 17 | (21.6) |
| 3-5 | 5 | (6.4) |
| 7-9 | 3 | (3.8) |
| No. (%) of High-Risk Follow-up Clinic visits during follow-up | p) | |
| None | 10 | (12.7) |
| 1-3 | 18 | (22.9) |
| 4-7 | 29 | (36.8) |
| 8-17 | 22 | (28.0) |

two-year follow-up period. (Two more infants who originally met study criteria were not included in the sample because their hospital records were destroyed when they died following discharge.) The causes of death for these eight infants were sudden infant death syndrome (n=2), meningitis/sepsis (n=1), meningococcemia (n=1), trauma (rat bites) (n=1), and unknown causes (n=3).

Table 3 shows the results of the hierarchical multiple regression. The three maternal sociodemographic variables entered first as a block failed to predict rehospitalization significantly. accounting for only 3% of the variance (using the adjusted R^2 value) in rehospitalization. In the next step, however, the addition of the two viability variables as a block resulted in a significant improvement in the model, which then accounted for 11% of the variance in rehospitalization. The regression coefficients for the individual variables indicate, however, that after the significant effects of birth weight were removed, gestational age had no effect on the prediction of rehospitalization.

| | Table | 3.—Regrei | ssion Results* | | | |
|---|-------------------------------------|--------------------------------------|-------------------------------|--------|---------------|---------|
| Variables | Adjusted R ² Value | Adjusted R ² Change | F Statistic Change (df) | В | SE of B | , |
| Block 1: maternal | .03 | | 1.89 (3,75) | | | |
| Marital status | | | | .20 | .45 | .45 |
| Education | . , , | | | 26 | .12 | -2.14† |
| Age | | | | .05 | .04 | 1.25 |
| Block 2: infant | .11 | .08 | 4.71 (5,73)‡ | | | * **** |
| Birth weight (in kg) | | *** | | - 2.08 | 1.05 | 1.981 |
| Gestational age | | | | 08 | .10 | 75 |
| Block 3: Medical | .30 | .19 | 11.02 (7,71)‡ | | | |
| High-Risk Follow-up Clinic (HRFC) visits | | | | .22 | .05 | 4.531 |
| Prenatal | | | | .15 | .11 | 1.28 |
| Quadratic terms HRFC | .45 | .15 | 21.09 (8,70)‡ | .04 | .007 | 4.59‡ |
| Education | .48 | .03 | 4.63 (9,69) | .06 | .03 | 2.15 |
| Prenatal | .51 | .03 | 4.36 (10,68)† | 10 | .05 | - 2.09t |

^{*}Variables were entered into the regression equation in the order listed in the table. The unstandardized regression coefficients and their associated standard errors and t values are those for the variables at their order of entry into the equation.

Addition of the third block of variables relating to the appropriate use of medical care (prenatal care and HRFC visits) again resulted in a significant improvement and a model that accounted for 30% of the variance in rehospitalization. The individual regression coefficients indicate that the number of HRFC visits was a significant predictor of rehospitalization, while the month in which the mother's prenatal care began was not significant. The sign of the HRFC variable indicates that the lower the number of HRFC visits, the greater the number of rehospitalizations.

At this point, an examination of the assumptions of linear regression using the residuals suggested that not all of the variables included in the model were linear in their effects on rehospitalization. Although one might postulate which variables might be nonlinear, because no firm evidence exists to suggest credible hypotheses, a stepwise procedure was used to add significant (P < .05) quadratic factors to the model.14 (This means that the computer selected the order of entry of the variables, based on the improvement in fit of the model.) A quadratic term, which is simply the square of a variable, indicates one bend in the

curve of the regression surface.

Three terms met the significance requirement for addition to the model. indicating curvilinear effects of these variables on rehospitalization. (The significance of the quadratic terms means that the regression coefficients for the lower order terms of those variables cannot be taken alone as the true effects of those variables on rehospitalization. 14) First, the addition of the quadratic term for the number of HRFC visits resulted in a significant adjusted R^2 change of 15% and a model that predicts 45% of the total variance. The positive sign of the regression coefficient indicates a relationship represented by a concave upward curve. 15 In other words, infants with both very few and very many HRFC visits (relative to the rest of the sample) had more rehospitalizations than infants with visits in the middle range.

Next, the addition of the quadratic term for maternal education resulted in an adjusted R^2 change of 3% and a model that accounts for 48% of the variance. The positive sign of the regression coefficient indicates a relationship represented by a concave upward curve, indicating that infants whose mothers had relatively low and

[†]P<.05, two-tailed.

[‡]P<.01, two-tailed.

high educational levels had more rehospitalizations than other infants.

Finally, the addition of the quadratic term for prenatal care resulted in an adjusted R^2 change of 4% and a final model that accounts for 51% of the variance in rehospitalization. The negative sign of the regression coefficient indicates a relationship with rehospitalization that is represented by a concave downward curve, with prenatal care beginning in the middle of pregnancy (relative to the sample) associated with increased rehospitalizations.

In most cases it is desirable to test a model on a new sample to determine its generalizability across samples. Failing that, one may "split" the sample, using half to construct the model and half to test it. Neither alternative was available in the present study. Therefore, data on the accuracy of the model in predicting the actual number of rehospitalizations for individual cases are as follows:

| Accuracy of | No. of |
|----------------------------|--------|
| Prediction | Cases |
| Correct ± 1 | |
| rehospitalizations | 57 |
| >1 to 2 rehospitalizations | 14 |
| >2 rehospitalizations | 8 |

The model correctly predicted (within one rehospitalization) the true number of rehospitalizations for 72.2% of the sample.

COMMENT

The results of this study suggest that it is possible to predict with reasonable accuracy which infants in this sample of VLBW infants would require rehospitalization in the first two years of life, using data widely available in medical records. Our model correctly predicted the number of rehospitalizations (within one) for over 70% of the sample. By virtue of our sample site, the current sample is a very disadvantaged, largely minority one; however, these results might not hold in other settings. In a population with greater diversity of race, income, and marital status, one might find that these sociodemographic variables are significant in predicting which infants will require rehospitalization.

Indeed, the curvilinear effect of ma-

ternal education on rehospitalization in this sample is surprising in view of consistent findings of an inverse relationship between maternal education and other socioeconomic indicators of an infant's early environment as well as a variety of poor pregnancy and parenting outcomes, including mental retardation and behavioral problems. ¹⁶ In the current study, infants whose mothers had either very little or a great deal of education (relative to this disadvantaged population) were at excess risk of rehospitalization.

It may be that mothers with high levels of education are so atypical among this disadvantaged sample that they represent a special population with unusual problems and needs. For example, contrary to what might be expected, of the highly educated (13 years or more of education) mothers in this sample, ten were single mothers. Two were drug abusers and two were in prison at the time of delivery. The reverse in expected life circumstances that led to these unlikely outcomes for women with high education may also be associated with increased rehospitalizations for their infants.

The significance of birth weight in predicting rehospitalization was not a surprise, of course; low birth weight also is the single best determinant of infant mortality. Many of the smallest of these infants would have died only a few years ago and now they survive only with considerable morbidity. Still, birth weight was not a perfect or even near-perfect predictor. Many very premature infants do go on to develop normally with no signs of problems. What is needed are predictors that would go beyond size and maturity at birth to determine which infants have the greatest risk of morbidity and rehospitalization.

The addition of the third block of variables signifying appropriate use of medical care may present such an opportunity, but the significance of the quadratic factor of these variables when entered later in the analysis complicates the interpretation of the significance of this block of variables. These results suggest that in the case of HRFC visits, infants at both the low and the high ends of the distribution are at excess risk of rehospitali-

zation. Infants at the low end of the distribution of HRFC visits may represent those who receive inadequate follow-up considering their vulnerability, while those with many visits probably were infants who were seen frequently because of chronic illness or because of their very fragile conditions.

In the case of prenatal care, the absence of a linear effect on rehospitalization was surprising in view of previous research and what is known about women who do not receive adequate prenatal care. The significance of the quadratic factor of this variable, however, indicates a significant nonlinear effect, and the sign of the regression coefficient for the quadratic term indicates that, contrary to logic, the infants whose mothers began prenatal care midway in pregnancy (relative to other mothers in this study) were at excess risk of rehospitalization relative to other infants. Inadequate prenatal care has been found in previous studies9 to be predictive of VLBW infant rehospitalization and may be indicative of either lack of knowledge regarding the appropriate use of preventive and primary care or the inability to use such care due to problems with transportation, access, and other factors.

The literature provides no suggestions for interpretation of these findings that infants whose mothers began prenatal care in the middle range of the distribution had more rehospitalizations than those whose mothers began care later in pregnancy. Again, it is possible that the mothers who began their care at this time were unusual in some other way. This finding clearly requires replication and further clarification.

It must first be emphasized that this study examines only one of many outcome variables. While rehospitalization is important in terms of both cost to the public and quality of life for the infants and their families, it certainly does not present a complete picture. These results nonetheless suggest two conclusions. First, HRFC personnel may want to monitor closely the early behavior of parents of NICU infants in complying with the follow-up protocol, especially when the

fants are at the low end of viability. Perhaps those who fail to keep appointments could be "flagged" early for intensive services such as home visits by a social worker or public health nurse or referral to a child protection agency. They may need assistance with transportation or instruction in the rationale for close follow-up of their infants. Parents who are clearly compliant with the suggested schedule perhaps could receive less intensive (and thus less expensive) services or even could be discharged to a knowledgeable community pediatrician, with case management by the regional center to ensure that other needed services are received (such as financial aid). While the HRFC does engage in aggressive follow-up within the limitations of understaffing and underfunding, such measures might be more productive if they began earlier and were more precisely targeted to the very-highrisk infants.

The second possibility suggested by

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these results concerns the effectiveness of high-risk follow-up itself. The current study was not an evaluation study, which would require quantification of the independent variable (the services provided in the HRFC) and the use of a control group; therefore, it is not possible to conclude that highrisk follow-up services are effective in preventing rehospitalization. It is possible that self-selection is the key variable, or is at least a very important factor, much as is self-selection in the positive impact of prenatal care on pregnancy outcome. That is, it may be that parents who adhere to the followup schedule prescribed for their infants are different from other parents (perhaps more knowledgeable or more concerned) and thus are more likely to have healthier infants who require fewer rehospitalizations.

It is also possible, however, that the follow-up services themselves contribute to the positive outcomes. Many of the infants in this sample who never or seldom attended the HRFC were in

the care of pediatricians in the community and so presumably received basic primary care such as immunizations, but many pediatricians feel unprepared to care for and deal with the special needs of high-risk infants.17 Moreover, normal pediatric primary care does not provide the comprehensive services, aggressive outreach, and work with other agencies and services provided by this multidisciplinary clinic, which includes public health nurses, social workers, physical therapists, and vision and hearing specialists. The extremely disadvantaged families in this sample had many problems and needs that would affect the health of these infants. While these results are suggestive of the value of multidisciplinary follow-up, further research must confirm the effectiveness of these services and of particular service components.

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Quotables:

Research: If we knew what we were doing, it wouldn't be research.

J. C. STAMOS

Perspectives in Biology and Medicine 1984

Body Image and Eating Behavior in Adolescent Girls

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 To determine attitudes toward body weight and shape and eating and weight control practices among adolescent girls, an anonymous questionnaire was administered to 854 adolescent girls and young women aged 12 through 23 years who were seen in a military adolescent outpatient clinic. Overall, 67% were dissatisfied with their weight, and 54% were dissatisfied with their body shape. Dissatisfaction with weight and shape varled positively with increasing body weight but not with increasing age. Binge eating had occurred in 30.4%, and weight control behavior, such as dieting, fasting, vomiting, and stimulant, laxative, and diuretic use, had occurred in 38.2%, 30.7%, 8.5%, 9.5%, 3.3%, and 6.2%, respectively, varying positively with increasing weight. Thirty-six percent of those adolescent girls who saw themselves as overweight desired an inappropriate weight loss, and 61% of these, who desired an excessive loss, exhibited an increased prevalence of weight control behaviors and were less likely to believe that they had an eating problem. Dissatisfaction with body weight and shape, and eating behaviors, such as dieting, binge eating, fasting, and vomiting, are common in adolescent girls, many of whom are attempting weight control without an accurate perception of what is normal.

(AJDC 1988;142:1114-1118)

Anorexia nervosa and bulimia are common subjects in the medical literature. 1-4 Most reports focus on patients who actually have these di-

agnoses or on methods for identifying such patients in the general population. The increasing prevalence of these conditions has been, in part, blamed on a societal and media emphasis on thinness and weight control as means of attaining physical attractiveness and acceptance. Attitudes toward body shape and weight have their roots in adolescence, perhaps even in childhood. To assess the degree to which contemporary adolescents are concerned with such issues, a large unselected group of adolescent females were studied cross-sectionally with regard to their attitudes toward body weight, body shape, and use of various eating and weight control behaviors.

PATIENTS AND METHODS

The subject population comprised 854 girls and young women aged 12 through 23 years who were seen for health care in a primary care adolescent clinic at a major military medical center between February and November 1984. The sample was largely middle class, comprising dependents of active-duty upper-echelon military personnel and dependents of civilian, formerly military personnel. The sample was predominantly white, with small numbers of black, Asian, and Hispanic patients. The subjects' height was measured to the nearest tenth of a centimeter on a Harpenden stadiometer, and their weight was measured in pounds (converted to kilograms) on a standard ballistic scale. Originally, 1000 anonymous questionnaires that inquired about attitudes toward body weight and shape, and whether or not certain eating or weight control behaviors had occurred, were distributed consecutively. The study population represented returned questionnaires, minus 49 questionnaires that were insufficiently complete. The questionnaire (Figure) contained 16 questions that were answerable by yes or no. Additionally, patients were allowed to volunteer information, such as amount of desired weight loss,

desired body part change, and frequency of eating behaviors, so that these answers would not be biased by suggestion (Figure). This study was approved by the institutional human subjects review board. Written informed consent was not deemed necessary by the institutional human subjects review board, since questionnaires were completed anonymously. Patients were told that the Adolescent Clinic was conducting a survey, but that participation was voluntary.

Patient data were organized into three groups based on weight for height for age according to US Department of Health and Human Services tables.⁵ Subjects were classified as underweight if they were less than the 25th percentile of weight for height, and overweight if they were greater than the 75th percentile of weight for height. Data were also analyzed by three age groups that roughly corresponded to educational level: junior high school (12 through 15 years), high school (16 through 18 years), and college/career (19 through 23 years). Distribution of weight groups was similar among the three age groups $(\chi^2 = 0.79, P = .94)$. Statistical analysis was carried out on a computer (IBM PC-AT) using the SPSS program. Data were analyzed descriptively, by χ^2 analysis and by test of proportions.

RESULTS Satisfaction With Weight

Overall, 67% of girls were dissatisfied with their current weight, although only 53% were not within the normal weight group. Only 4% of the sample believed that they were underweight, whereas 12% actually fell into the underweight group. There was also a difference between perceived and actual overweight; 63% believed that they were overweight, but only 40% fell into the overweight group. When analyzed by weight group, 92% of overweight girls were dissatisfied with their weight, but 53% of normal weight girls were also dissatisfied with their

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| | ATING ATTI | TUDE SURVE | Y | |
|---|----------------|------------------|---|-----------------|
| GE SEX | | HEIGHT | jų. | WEIGHT |
| O YOU THINK YOU EAT AN ADEQUATE SELECTION AN | D AMOUNT OF | 1 | | R BODY WEIGHT? |
| Li Yes Li No | | | Yes | □ No |
| f no, list below any problems you feel are from not eati | ng correctly: | if no, do you fe | el that you are: | |
| | | □ to | thin. Need | to gainjbs. |
| | | П то | ofat. Need to | Inse the |
| ###################################### | | | | |
| RE YOU SATISFIED WITH YOUR BOOY SHAPE! | | 1 | | |
| ☐ Yes ☐ No | | | | |
| f no, list below any areas that you would like to increas | e or decrease: | | | |
| Increase: | | Decreas | e: | |
| | | | | |
| | | | *************************************** | |
| | | | *************************************** | |
| RE YOU INVOLVED IN SCHOOL ATHLETICS? | | DO YOU HAVE Y | OUR OWN EXE | RCISE PROGRAM! |
| Yes No | | | ☐ Yes | □ No |
| f yes, which sport/sports are you involved in: | | If yes, describe | your program b | elow: |
| | | | | |
| | | | | |
| AVE YOU EVER BEEN ON: | | 1 | ······································ | |
| A weight loss diet? | ☐ Yes | [| □ No | |
| A weight gain diet? | ☐ Yes | (| □ No | |
| A sports training diet | ? 🗆 Yes | Ε | □ No | |
| O YOU OR HAVE YOU EVER DONE ANY OF THE FOLLO | NING? | | | |
| Binge eat (eat large amounts of food without stop | | ☐ Yes | □ No | Times per month |
| Binge drink (Alcohol) | , ,,, | ☐ Yes | □ No | Times per month |
| Fast (no food for 24 or more hours) | | ☐ Yes | □ No | Times per month |
| Make yourself vomit after eating | | ☐ Yes | □ No | Times per month |
| Use laxatives to control weight | | ☐ Yes | No | Times per month |
| Use diuretics to control weight | | ☐ Yes | □ No | Times per month |
| Use stimulants (uppers, amphetamines) to control | appetite | ☐ Yes | □ No | Times per month |
| Eat only certain kinds of food | | ☐ Yes | □ No | Times per month |
| If yes, list what kinds of foods: | | | - | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| O YOU THINK YOU HAVE ANY PROBLEMS CONNECTED | WITH EATING! | | | |
| Yes No | | | | |

Anonymous questionnaire administered to 854 adolescent girls and young women aged 12 through 23 years, to determine attitudes toward body weight and shape and eating and weight control practices.

weight. Only 40% of underweight girls were dissatisfied with body weight (Table 1).

Of those girls who perceived themselves as overweight, 93% (n = 498) wrote down the amount of weight that they wanted to lose. The desired weight loss was appropriate in 64.5% (n=321) of these and inappropriate in 35.5% (n = 177) (Table 2). Within the group that desired an inappropriate weight loss, 61% (n = 108) desired an inappropriately large (into the underweight category) weight loss, and 39% (n=69) desired an inappropriately small (still within the overweight category) weight loss. When analyzed by weight group, 82% (89/108) of those girls who desired an excessive weight loss were not overweight to begin with, and 16% (n = 17) were actually underweight. Conversely, of those girls who were overweight, 24% (n=69) indicated a target weight that was still within the overweight range.

Dissatisfaction with body weight was prevalent at all ages, but greatest in the high school group (Table 1). Among girls who wished to lose weight, a greater proportion of the high school group (56 [24.6%] of 228) desired an excessive weight loss,

whereas a greater proportion of the college/career group (19 [17.9%] of 106) desired an insufficient weight loss when compared with other age groups (Table 2),

Satisfaction With Body Shape

Of the entire sample, 54% (n = 461) of girls did not like their body shape. This was true of 75% of overweight girls, but also of 44% of normal weight girls (Table 1). As with body weight, dissatisfaction with body shape was highest among high school girls (Table 1). Of those girls dissatisfied with body shape, 74% (n = 340) wrote in the body parts that they would like to change. Of these, 68% (n = 231) wished to reduce their thigh size. Other areas of desired loss were abdomen (38%), hips (36%), waist (25%), and buttocks (16%). Of body areas that they desired to become augmented, breasts were most commonly listed (14%).

When analyzed by weight group, the highest priority of overweight and normal weight girls was to decrease thigh size, but the proportion of girls who desired to do this was greater among normal weight than overweight girls. The highest priority of underweight girls was to increase breast size. However, one third of underweight girls desired to decrease thigh size.

Eating and Weight Loss Behaviors

There was one eating behavior (binge eating) and six weight control behaviors (dieting, fasting, vomiting, and laxative, diuretic, and stimulant use) listed on the questionnaire (Table 3). Overall, 38% had attempted a weight loss diet at some time, with an increased prevalence by age group and weight group (P < .001). Thirty percent had indulged in binge eating; the prevalence was highest in high school girls. Prevalence of binge eating increased significantly with increasing weight (P<.025). Of those girls who had binged, 67% had done it at least monthly and 23% at least weekly. A related behavior, binge drinking (alcohol), had occurred in 11%; the prevalence increased with both age and weight. Of those girls who had indulged in binge drinking, 52% did so monthly and 28% weekly. A high proportion of binge drinkers (54%) had also engaged in binge eating.

Fasting behavior (>24 hours) had occurred in 31% of the total sample; it was most prevalent in high school girls and rose significantly with weight (P < .001). Of those girls who had fasted, 53% did so at least monthly and 11% weekly. Self-induced vomiting had occurred in 8.5% of the sample; within this group, 42% did so monthly and 16% weekly. Similarly, stimulant use to lose weight had occurred in 9.5%; 43% of this group did so monthly and 17% weekly. Prevalence of stimulant use was also highest in high school girls and increased significantly with weight (P < .001). Laxative and diuretic use were less common (3% and 6% of the sample, respectively). Prevalence of these behaviors increased with weight but not age.

When behaviors were analyzed according to whether subjects were either satisfied or dissatisfied with body weight or shape, the proportion who exhibited the behavior was higher in those subjects who were dissatisfied (Table 4). Among subjects who desired to lose weight, those who desired excessive weight loss were more likely to have indulged in binge eating, fasting, self-induced vomiting, and stimulant use, and less likely to have tried a weight loss diet, when compared with those subjects who desired an appropriate loss. Prevalence of other behaviors was small in both groups.

Overall, 31% of girls thought that they had a problem related to eating. This perception was most prevalent among overweight girls and high school girls (Table 1) and among girls who exhibited weight control behaviors. There was a significant increase in the perception of a problem related to eating among girls who were dissatisfied with body weight or shape (P<.01) (Table 4). Interestingly, among girls who desired to lose weight, the greatest perception of having an eating problem occurred in the group with insufficient weight loss, and the lowest perception of having an eating problem occurred in the group with excessive weight loss.

COMMENT

Although the sample in this study may appear to be somewhat biased by its selection from a military clinic population, there are some aspects that make it more representative of the population at large. Since care is free, there is no financial disincentive to use the clinic, and it is used more liberally by all socioeconomic classes. Patients are seen for minor complaints, as well as for routine physical examinations; thus, many healthy adolescents pass through the clinic. The population is not strictly military; many of the parents are civilians, and they are presumably as representative of the general population as any other groups of civilians.

The data in this report indicate significant dissatisfaction with body weight, and, to a lesser extent, dissatisfaction with body shape, among normal and underweight adolescent girls. This is consistent with a societal pre-

occupation with weight and thinness. Dissatisfaction is highest during high school years. There are several possible explanations for this. Midadolescent girls may be more body and peer conscious during these years than later. The older group in this study was less homogeneous, since it was composed of both girls who were in college and those who were working and perhaps less exposed to peer pressure and group norms. Finally, the peak could indicate an increasing concern with body image among younger girls in general, which will be reflected in the older age group in three to five

There is either a significant ignorance of or distortion of awareness of body norms for body weight, manifested by the 36% of girls desiring weight loss who had inappropriate

Table 1.—Satisfaction With Body Weight and Shape and Perception of Eating Problem According to Weight and Age*

| | | % (N = 854) | | | |
|--------------|-----|------------------------------|-------------------------------------|------------------------------------|---------------------------|
| | n | Distribution of Sample | Dissatisfied With Body Weight | Dissatisfied With Body Shape | Problem With Eating |
| Weight group | | | | | |
| U | 104 | 12.2 | 40.0 | 26.0 | 23.2 |
| N | 405 | 47.4 | 53.1 | 44.4 | 21.8 |
| 0 | 345 | 40.4 | 92.2 | 74.8 | 42.4 |
| Age group | | | | | |
| JH | 319 | 37.3 | 62.3 | 48.0 | 24.6 |
| HS | 357 | 41.8 | 70.7 | 60.2 | 35.8 |
| CC | 178 | 20.8 | 69.0 | 54.5 | 30.2 |

^{*}U indicates underweight; N, normal weight; O, overweight; JH, junior high school; HS, high school; and CC, college/career.

Table 2.—Perception of Proper Amount of Weight
Loss Among Subjects Desiring to Lose, According to Weight

| | n | Desired Weight Loss (N = 498) | | | | |
|--------------|-----|-------------------------------|-------------------------|------------------|--|--|
| | | | Inappropriate (n = 177) | | | |
| | | Appropriate | Excessive | Insufficient | | |
| Weight group | | | | | | |
| U | 17 | 0 | 17 | 0 | | |
| N | 190 | 118 | 72 | 0 | | |
| 0 | 291 | 203 | 19 | 69 | | |
| Total (%) | 498 | 321 (64.5) | 108 (21.7) | 69 (13.8) | | |
| Age group | | | | | | |
| JH | 164 | 106 | 35 | 23 | | |
| HS | 228 | 145 | 56 | 27 | | |
| CC | 106 | 70 | 17 | 19 | | |
| Total (%) | 498 | 321 (64.5) | 108 (21.7) | 69 (13.8) | | |

*U indicates underweight; N, normal weight; O, overweight; JH, junior high school; HS, high school; and CC, college/career.

goals. The fact that 82% of the girls who wanted to lose weight were not overweight to begin with indicates that an unrealistic ideal of appropriate weight exists for many adolescent girls. The 24% of overweight girls whose desired weight loss was insufficient likewise demonstrates a poor perception of what constitutes normal body weight. Both of these findings may reflect a larger societal failure to define or agree on what is appropriate.

Among age groups, the larger proportion of high school girls who desired an excessive loss reinforces the concept that midadolescent girls may be more appearance conscious and more influenced by perceived societal ideals. The finding that the college/career group contained the greatest proportion of subjects who desired an insufficient weight loss when compared with other ages may reflect a diffusion of or lack of reinforcement of peer group norms in this heterogeneous group, so that individuals are less aware of what is considered normal.

All weight control behaviors increase with age from junior high school to high school, but with the exception of weight loss dieting, there is little change from high school to college/career age. In a cross-sectional study, such as this, one would expect total prevalence to increase with age, unless the incidence was actually higher in a younger age group. The lack of difference suggests that there is an increasing involvement in eating and weight control behaviors at younger ages. All behaviors also increase with the weight group; this is

in agreement with the findings of Halmi and colleagues.

Johnson and colleagues⁷ reported similar data on 14- to 18-year-old American girls in 1983. The current population exhibited a higher perception of being overweight (63% vs 48%) and a lower perception of being underweight (4% vs 8%). This may indicate a decreasing tolerance for actual weight and an increasing desire for thinness since 1983. However, the lower weight dissatisfaction in the study by Johnson and colleagues7 may be related to the fact that only 19% of their population was classified as overweight vs 40% of the current one. Furthermore, they used 110% of average weight for age, without taking into account height, as their definition of overweight, so that the data are not strictly comparable.

Brennan and Kevany^s found that 61% of Irish adolescent girls wanted to lose weight, a figure similar to the

63% found in the current study. This figure is also comparable with the 70% reported by Miller and colleagues. In the Irish study, 16% of underweight girls wanted to lose weight (vs 16% in this study), but 69% of normal weight girls (vs 47%) wanted to lose weight, suggesting an even greater weight consciousness among Irish adolescents. In agreement with the study results found by Brennan and Kevany and Miller et al, the highest priority for body part change was to decrease thigh size.

The frequency of behaviors, such as binge eating and self-induced vomiting, in this study falls between those previously reported, which range from 27% binge eating monthly and 7% vomiting monthly in the study by Johnson et al,⁷ to 5% binge eating monthly and 0.7% vomiting monthly in a study of New Zealand teenage girls by Wells and colleagues.¹⁰ Killen and colleagues,¹¹ in a study of Ameri-

Table 3.—Involvement in Eating and Weight Loss Behaviors
According to Weight and Age*

| | % of Each Weight or Age Group Having Tried: | | | | | | | |
|--------------|---|-----------------|-------------------|----------------|----------|------------|-----------|-----------|
| | Diet | Binge Eating | Binge Drinking | Fasting | Vomiting | Stimulants | Laxatives | Diuretics |
| Weight group | | | | | | | | |
| U | 12.9 | 20.6 | 7.2 | 21.4 | 5.2 | 1.1 | 2.1 | 0.0 |
| N | 30.8 | 28.2 | 10.3 | 24.3 | 7.5 | 7.6 | 3.1 | 5.4 |
| 0 | 54.8 | 36.0 | 12.7 | 40.7 | 10.5 | 14.3 | 4.0 | 8.9 |
| Age group | | | | 14 (14 A) 14 T | | | | |
| JH | 30.8 | 23.5 | 4.9 | 17.8 | 6.9 | 5.0 | 2.6 | 2.0 |
| HS | 40.7 | 36.3 | 13.0 | 38.9 | 10.1 | 13.0 | 3.6 | 8.6 |
| CC | 46.0 | 31.2 | 17.5 | 37.2 | 8.1 | 10.6 | 4.1 | 8.8 |

*U indicates underweight; N, normal weight; O, overweight; JH, junior high school; HS, high school; and CC, college/career. N = 854.

Table 4.—Involvement in Eating and Weight Loss Behaviors According to Satisfaction With Body Weight and Shape and Appropriateness of Desired Weight Loss

| | | % Having Tried: | | | | | | | | |
|-----------------|-----|-----------------|-----------------|-------------------|---------|----------|------------|-----------|-----------|---------------------------|
| | n | Diet | Binge Eating | Binge Drinking | Fasting | Vomiting | Stimulants | Laxatives | Diuretics | Problem With Eating |
| Weight | | | | | | | | | | - |
| Satisfaction | 280 | 16.1 | 18.5 | 6.9 | 15.2 | 2.7 | 1.9 | 0.4 | 8.0 | 14.0 |
| Dissatisfaction | 574 | 48.9 | 35.9 | 13.0 | 38.0 | 11.1 | 13.2 | 4.8 | 8.9 | 38.5 |
| Shape | | | | | | | | | | |
| Satisfaction | 389 | 23.2 | 19.4 | 8.5 | 18.1 | 3.0 | 3.0 | 1.4 | 1.7 | 17.2 |
| Dissatisfaction | 465 | 50.5 | 39.7 | 13.1 | 41.1 | 13.0 | 15.0 | 5.0 | 10.0 | 41.5 |
| Weight loss | | | | | | | | | | |
| Appropriate | 321 | 52.1 | 36.0 | 11.7 | 37.7 | 8.4 | 13.2 | 4.6 | 11.1 | 38.4 |
| Excessive | 108 | 47.2 | 41.2 | 13.7 | 44.7 | 20.6 | 16.8 | 6.8 | 5.9 | 30.4 |

can tenth-grade girls, reported prevalences of 10.6% self-induced vomiting, 8.3% use of diet pills, 6.8% laxative use, and 3.6% diuretic use. In comparison, the current high school age group had a similar prevalence of vomiting, but slightly higher prevalences of stimulant and diuretic use.

Another weight control behavior, 24-hour fasting, has not usually been studied in conjunction with the bingepurge behaviors. This behavior occurs with the same frequency as binge eating and, after dieting, is the most common weight control behavior noted in this population. It occurs with a higher prevalence among girls who binge eat (45.2%) than among those who do not (24.2%). The increased prevalence of a weight control behavior, such as fasting, among girls who are dissatisfied with body weight or shape and its linkage with binge eating suggests that this behavior is, to some degree, more likely to be employed as a way to change body weight or shape than to be a random occurrence.

Attitudes and behaviors of girls aged 12 through 14 years have been studied little. Data from junior high school girls in this study indicate that all of the behaviors observed in older adolescent girls also exist in this age group. Almost one third have already attempted dieting, and nearly one fourth have engaged in binge eating. Fasting is also the most common weight control behavior, after dieting, in this group.

A subgroup of adolescent girls who have inappropriately low weight goals were identified. This group may have a distortion of both body image and eating behavior, as reflected by the increased prevalence of binge eating, fasting, and self-induced vomiting.

The study was not designed to detect anorexia nervosa or bulimia; however, given appropriate environmental and psychologic circumstances, this group appears to be at higher risk for these disorders, in view of their lower perception that they might have an eating problem.

CONCLUSION

There is an increasing awareness in the medical community that adolescents and young adults constitute a group that has special health care needs and has been underserved in the past. 12 Clinicians who treat adolescents and young adults should be aware that there is a high prevalence of dissatisfaction with body weight and shape among females already by the time of early adolescence. This dissatisfaction appears to be accentuated during high school years, and a significant proportion of girls are not only making attempts to lose weight, but more than one third of those who wish to lose weight do not have a realistic idea of how much is proper to lose. To do so, they may indulge in behaviors, such as dieting, fasting, binge eating, and vomiting, which may affect both their nutrition and health.

Clinicians who are involved in health maintenance provision for adolescents and young adults should inquire about their patients' body weight and shape satisfaction. If the patient admits to dissatisfaction, further history should be obtained to delineate whether the patient has unrealistic goals for weight change, is involved in behaviors that are potentially adverse to good health, or believes that she has a problem related to eating. Although few patients will actually have anorexia nervosa or bulimia, some may be benefited by early intervention and proper education regarding detrimental eating behaviors and appropriate body weight. Likewise, they can be instructed in appropriate weight loss goals and means of losing weight if weight loss is indicated.

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Management of Traumatic Hyphema in Children: An Analysis of 340 Cases Risto J. Uusitalo, MD; Leena Ranta-Kemppainen, MD; Ahti Tarkkanen, MD (Arch Ophthalmol 1988;106:1207-1209)



Disorders of Higher Cerebral Function in Preschool Children

First of Two Parts

Isabelle Rapin, MD

This excellent review by Dr Rapin will appear in two parts, in successive issues of AJDC.—Ed.

 In preschoolers, disorders of higher cerebral function are most likely to present as inadequate development of language, while in school-age children, learning disabilities and attention deficit predominate. The main considerations in the differential diagnosis in preschoolers with inadequate language are hearing loss, mental deficiency, dysphasia, and autistic spectrum disorders. Attention to the child's ability to engage in symbolic play and communicate meaningfully is the key to this often baffling differential diagnosis. With the exception of definitive assessment of hearing, classic medical investigations are seldom informative because structural brain lesions and metabolic errors are much rarer etiologies than prenatal and genetic influences on brain development. While many children improve with age, the underlying deficit(s) usually persists. The role of the physician is to detect the developmental problem, give the parents a correct diagnosis, refer the child for appropriate investigation and intervention, and provide follow-up and counseling. Early diagnosis is essential for effective remediation.

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The developmental disorders of higher cerebral function in children are commonly seen in office practice but often pose problems for physicians with little training in this field. Physicians' misconceptions may impair

their ability to evaluate the children effectively and to provide judicious advice to parents. This article focuses on the disorders most likely to present in preschool children, namely, mental deficiency, the developmental language disorders, and the autistic spectrum disorders. In school-age children, learning disabilities and disorders of attention predominate.

GENERAL CONSIDERATIONS

The term minimal brain dysfunction or damage (MBD) is often applied to children without gross motor deficits or mental deficiency who lag in some aspect of development. This term has outlived its usefulness because of its vagueness; it is more helpful to define which brain systems are involved (Table 1).

Etiology

There is no one specific etiology for any of these disorders. In most cases the cause is unknown. Prenatal and genetic etiologies seem to predominate over acquired insults to the developing brain as a result of prematurity, perinatal anoxia or trauma, and postnatal illnesses. For example, there are families whose particular variant of dyslexia has been linked to chromosome 152; girls with Turner's syndrome³ and children with Williams syndrome4 tend to have severe visualspatial deficits in the face of adequate verbal skills. The fact that boys are affected much more often (4:1) than girls reinforces the probability that exogenous insults to the brain are unlikely to be responsible for the majority of cases.

Pathophysiology

Whether delayed acquisition of complex skills, such as speaking and read-

ing, is the clinical expression of delayed brain maturation or of a permanent deficit in brain structure or organization-often referred to as a static encephalopathy-remains a subject for debate. This controversy arises because the defective skills of many children improve with age, and because children acquire skills in variable order and at variable ages. Deciding when a child is normal but immature and when he is truly deviant is therefore difficult. Detailed neuropsychologic testing after a child has mastered a previously defective skill regularly shows that the deficit(s) presumed responsible for the earlier problem persists and that the child is using atypical cognitive strategies to achieve mastery. Postmortem examination of a few brains of dyslexic⁵ and autistic6 children revealed subtle abnormalities at the cellular level, such as neuronal migration defects, disorganization of cortical architecture, and increased cell packing density. Speaking of delay in the face of discernible microscopic defects in the brain is patently incorrect.

The brain has many redundant systems and its organization has considerable plasticity and potential for remodeling, especially during development. This accounts for the surprising resiliency of children's cognitive functions in the face of damage⁷ and for the fact that individuals may use different strategies to achieve a particular behavioral goal. The evidence today is that in many if not all children the "developmental" disorders of higher cortical function reflect subtle organic brain pathology rather than delayed maturation.

Children with overt sensorimotor deficits and those with demonstrable lesions on neuroimaging of the brain

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| Function | Type of Disorder | | | | |
|-----------------------------------|--|--|--|--|--|
| Motor programming and execution | "Soft signs," clumsiness Dyspraxias* | | | | |
| Sensory and perceptual experience | Visual-spatial deficits Auditory processing deficits "Cortical" sensory deficits | | | | |
| Arousal and attention | Disorders of alertness and sleep Attention deficit disorders/hyperkinesia | | | | |
| Language Oral Written | Dysphasias Dyslexias, other "learning disabilities" | | | | |
| Memory and learning | Amnesic disorders, anterograde amnesia Retrieval disorders | | | | |
| Affect, drive, socialization | Mood disorders Disorders of impulse control Autistic spectrum disorders | | | | |
| Cognition | Mental deficiency | | | | |

*It is customary to speak of dysphasia, dyslexia, and dyspraxia when considering inadequate acquisition of speech, reading, and praxis (programming of complex motor acts) and of aphasia, alexia, and apraxia when referring to acquired disorders of these skills after they have been mastered.

are regularly excluded from studies of the specific disorders of higher cerebral function, even when they have problems similar to those of children without overt pathology. Besides the fact that children with sensorimotor deficits are difficult to test with standard psychological instruments, this exclusionary practice stems from a desire to understand the pathophysiology of "pure" disorders and from the idea that pure disorders may have a specific etiology. While it is true that most children with pure behavioral syndromes do not have overt abnormalities on computed tomographic (CT) scans, improved neuroimaging techniques are disclosing subtle structural brain abnormalities in an increasing number of these children. 9,10 Of course, a normal CT or magnetic resonance (MR) scan does not exclude a structural brain anomaly, and even less a neurotransmitter or other biochemical deficit, since the resolution of neuroimaging does not extend to the cellular level.

PURE VS COMPLEX DISORDERS

"Pure" disorders are rare because most cerebral pathologies are unselective and because complex skills, such as calculating and playing the piano, call for the integrated activity of many brain systems. Therefore, the individual child often has a disorder affecting more than one system (eg, dyslexia plus attention disorder, attention disorder plus motor clumsiness). Disorders such as dysphasia^{11,12} and dyslexia^{12,15} can result from a variety of different cerebral deficits, and there are a variety of different subtypes of dysphasia, dyslexia, dysealculia, and other disorders characterized by different neuropsychologic deficits. It is important to group children with similar deficits into homogeneous subtypes if one wishes to discover the cerebral basis of these syndromes and to provide children with effective syndrome-specific remediation.

In summary, particular behavioral syndromes have a variety of etiologies. What counts is which brain system is dysfunctional, not the etiology of what made it dysfunctional. It is true, nonetheless, that the behavioral deficits resulting from a specific genetic etiology are likely to be quite similar in different children. Because children do not grow up in a vacuum, one needs to keep in mind that environment and remediation alter the phenotype of even single gene defects.

MENTAL DEFICIENCY

The term mental deficiency refers to overall behavioral incompetence. I prefer this term to mental retardation because retardation implies delay and the possibility of catch-up. While some mildly retarded children may have been educationally, culturally, and otherwise environmentally deprived and have the potential for catch-up, more seriously affected children have devi-

ant brains and will not catch up. This statement does not negate the fact that even significantly mentally deficient children learn new skills as they mature, that they can be taught remedial strategies, and that effective intervention helps alleviate many maladaptive behaviors.

Mental deficiency (mental retardation) refers to a static deficit of intellectual capacity. If it results from brain maldevelopment or a condition acquired in early life, it will preclude normal cognitive development. Diffuse brain insults sustained in later childhood may also produce mental deficiency. It is essential to differentiate mental deficiency from dementia, which refers to a progressive loss of previously acquired cognitive skills. Dementia is often difficult to differentiate from mental deficiency in very young children or when the loss of intellectual function is insidious.

Mental deficiency may reflect either diffuse or multifocal dysfunction of the brain. So-called "specific" disorders of higher cerebral function reflect more circumscribed dysfunctions. To diagnose a "specific" developmental disorder, one must be able to show that the child has areas of competence as well as areas of incompetence. Many children have more than one disorder of higher cerebral function. Children who have several may have so few areas of competence as to fall within the realm of mental deficiency. 16

The Concept of the IQ

The Intelligence Quotient, or IQ, is a summary score of subtest scores on standardized test batteries deemed to sample a sufficiently broad range of verbal and nonverbal behaviors to provide an adequate and representative measure of cognitive competence. The IQ score construct was developed to enable one to determine how much a given child's score deviates statistically from the mean score of his or her normal peers. The IQ can also be conceived as the ratio of mental age to chronological age. It is debatable whether the IQ is the most meaningful way to evaluate intelligence, if intelligence refers to successful problemsolving ability and adaptation to life rather than to what it is IQ tests measure.¹ No IQ battery assesses all cognitive skills and personality variables relevant to success in adult life. Nonetheless, the IQ is the most widely used means for gauging cognitive ability, and mental deficiency is regularly defined as a low score on an IQ test. Because humans have a wide variety of cognitive skills that are not necessarily tightly correlated, it is obvious that to use a single test or subtest to assess intelligence is fraught with the danger of an erroneous estimate of competence.

There are several problems with assessment of the IQ in pathologic populations. The IQ is not a valid measure of competence when there is focal or selective brain dysfunction that interferes with some skills but not others, when there are sensorimotor deficits that prejudice test taking, when there are linguistic barriers to comprehension and expression, when tests are used in populations other than those on which they were standardized, when less than the full test battery is administered, and when the child cannot or will not cooperate. The IQ construct implies that IQ is stable over time. This would only be true if the same mental capacities were sampled at each age, which is not the case during the early childhood vears when many mental capacities have not yet matured. In individual preschoolers especially, the IQ is a better measure of current level of function than a predictor of future competence. There are many test batteries yielding IQs from which to choose, but since they differ in their content and measure somewhat different cognitive skills, they may yield different IQ scores in the same child.17 This is especially likely to be the case in handicapped children whose handicap may penalize them unevenly for different tasks.

Neuropsychologic testing is not concerned as much with the overall IQ as with providing an inventory of the child's cognitive strengths and weaknesses across a broad range of skills. Neuropsychologic test results are often used to infer the localization of the child's underlying brain deficits, reasoning by analogy with the patterns

of impairment produced by acquired brain lesions in adults. Inferences based on these neuropsychologic test results are quite hypothetical because validating evidence from neuroimaging or electrophysiologic studies is rarely forthcoming in children with developmental disorders of higher cerebral function. Neuropsychologic test profiles are useful for grouping children with similar deficits so as to provide educators with specific information about the children's cognitive strengths and weaknesses. This is crucial if one wants to tailor remedial approaches to each child's particular cognitive handicap.

Levels of Mental Deficiency

The American Academy on Mental Retardation (formerly, on Mental Deficiency) has defined several ranges of mental deficiency based on the results of IQ tests but stresses that both IQ and adaptive ability must be considered when assigning a child to a particular level of mental deficiency (Table 2). These levels are useful for predicting the type of intervention the child requires and whether he is likely to be able to lead an independent life as an adult. One must be aware of pitfalls, such as testing a dysphasic child with a language-loaded test like the old Stanford-Binet, which did not yield separate verbal and performance IQs or subtest scores. In general, the verbal IQ is a better predictor of success in school than the performance IQ. It is important to look at subtest scores because both marked discrepancy between verbal and performance IQs and wide scatter among subtests scores suggest specific cognitive deficits rather than an underestimate of the child's potential, as often stated in psychologic test reports.

Memory and Learning

Intelligence is as much a function of what has been learned from experience as of the innate ability to solve problems efficiently. Children with mental deficiency learn less efficiently than normal children, and those with normal intelligence but circumscribed deficits in language and scholastic skills are regularly referred to as

| Table 2.—Level of Mental Deficiency as Estimated by IQ Testing ¹⁹ | | | | |
|--|------------------------------|--|--|--|
| Severity of Mental Deficiency | IQ Range | | | |
| Borderline | 71-80 | | | |
| Mild | 50-55 to approximately 70 | | | |
| Moderate | 33-40 to 50-55 | | | |
| Severe | 20-25 to | | | |

*The American Academy on Mental Retardation (formerly, on Mental Deficiency) stresses that adaptive skills, as well as IQ, be considered when assigning a child to a particular level of mental deficiency.

Profound

35-40

"learning disabled." Thus, a discussion of cognitive deficits that did not consider learning would be inadequate.

Learning refers to the long-term storage of skills and meaningful experiences that can modify current behavior. Determining what is meaningful requires an immediate memory store or buffer for the preliminary appraisal of current experience.²⁰

There appear to be at least two different memory systems: procedural memory, which has to do with remembering how to do things, and episodic memory, memory for particular events or facts. Amnesia or the inability to retain in memory or retrieve new items refers to a deficit in episodic memory. These two memory systems depend on different brain systems.

The immediate memory store has a span of only five to seven items and lasts a very short time (usually seconds at most) unless rehearsal takes place. This span is just long enough to enable one to decide whether new material is worthy of being further analyzed in an intermediate working or short-term memory, acted on, and stored in long-term memory. Immediate memory is highly dependent on attention and decays in seconds to a few minutes; short-term memory decays in minutes to a few days. Immediate verbal memory is tested by asking the child to repeat a string of words or numbers or a sentence he has just heard, while short-term memory is assessed after a delay of at least several minutes occupied by other activities.

Consolidation into long-term memory, in most cases, takes a very long time (hours to days) because it probably depends on synaptic alteration. Long-term memories are extremely resistant to erasure. In general, memories have a sensory tag so that there are visual, auditory, olfactory, and somatosensory memory stores. Memories are structured in long-term stores so as to be accessible through multiple channels. Memories are often chained. so that evocation of the first item of the chain elicits the other items of the sequence. Inability to remember is more often due to a deficit of retrieval from long-term stores than to one of storage, provided the material was once stored (ie, learned). Tests of vocabulary and information are tests of what has been stored in long-term memory, as well as tests of language and cognition.

While memories seem to be widely distributed in both cerebral hemispheres-in the sense that focal lesions do not produce discrete holes in memory—the ability to store and retrieve from long-term storage depends on the integrity of limbic circuits. These consist of the hippocampus, fornix, certain thalamic and brain-stem nuclei, as well as the hypothalamus and amygdala, which are concerned with evaluating the significance of ongoing events. It is of course no coincidence that the affective valence of experiences determines in part whether they will be stored and that the limbic system is concerned both with learning and with drive and affect. Bitemporal lesions, as a result of herpes simplex encephalitis for example, may produce a permanent anterograde amnesic syndrome in which new memories are not laid down even though old ones remain retrievable. Cerebral concussion as a result of trauma is the most common cause of transient interference with learning. Concussion interferes with the laying down of fresh memories; this produces a retrograde amnesia for events leading up to the accident by interfering with memories in the process of consolidation. Concussion also produces an anterograde amnesia for events immediately following the concussion because of transient interference with the laying down of new memories.

It is doubtful how often "learning disabilities" are due to inability to learn per se. Disorders of perception, language, conceptual organization, or other cognitive abilities are more often at fault. While some mentally deficient children have good rote memories, intelligence implies the ability to organize long-term memories into efficient networks that integrate newly stored memories creatively with old ones.

DEVELOPMENTAL LANGUAGE DISORDERS (DYSPHASIAS)

Besides delay in the acquisition of motor milestones, inadequate development of speech is the most common sign of a disorder of cerebral function in toddlers and preschool children. The differential diagnosis includes the following four main items: (1) hearing impairment, (2) mental deficiency, (3) dysphasia, and (4) autism.

Other disorders to consider but that present a less difficult differential diagnosis (Table 3) include structural abnormalities of the mouth and larynx, dysarthria (a motor disorder of the orofacial muscles that affects licking, swallowing, and breathing as well as speech and which, in its most extreme form, may cause aphonia), and elective mutism (a diagnosis applied to children who are mute in some environments and who speak well in others; it is essential to have a recording of the speech of such children to verify this diagnosis since some electively mute children have language disorders, while others are significantly emotionally disturbed).

The first item to consider is always hearing loss because missing this diagnosis would cause significant harm to the child who needs to be provided with hearing aids and to be exposed to visual language at the language-learning age. No child is too young or too handicapped to have hearing assessed definitively, using brain-stem evoked responses to complement and validate behavioral test results. It is never enough to rely on the parents' impression of normal hearing or on the physician's screening in the office.

Mental deficiency is a common cause for delayed and/or inadequate language development, although only se-

Table 3.—Differential Diagnosis of Inadequate Language Development

Hearing loss
Mental deficiency
Developmental language disorder
(dysphasia)
Autistic spectrum disorder
Elective mutism
Dysarthria
Structural abnormality of the upper
respiratory tract

Table 4.—When to Be Concerned With Inadequate Language Development

No meaningful words by age 18 months No meaningful phrases by age 24 months Speech unintelligible out of context at age 3 years

Noncommunicative use of language Inability to express specific wants Impaired comprehension

vere mental deficiency precludes it altogether. Less than severely mentally deficient children who are mute are almost always dysphasic and/or autistic as well. Autism, which is discussed in part 2 of this article, is much more common than generally appreciated; autistic children are communicatively impaired and often, but by no means always, mentally deficient.

Developmental dysphasia is one of the most common disorders of higher cerebral function to present in the toddler or preschooler. Because of the hypothesis that slow language development is caused by immaturity rather than deviance, many physicians are prone to reassure parents who complain that their child is not acquiring language as fast as they had expected. While this was perhaps acceptable in the days before the availability of intervention programs for very young children, it is not today.

Language learning starts at birth.²¹ The neonate is born able to make auditory discriminations relevant to language. By age 1 year, the infant has increased awareness of those relevant to the language or languages to which he is exposed and has decreased ability to discriminate others that occur in languages he has never heard.²² By a few months of age, the infant has already acquired many of the rules of conversation, such as looking at the

person who is speaking to him, smiling responsively, and turn taking with that person in cooing and, later, babbling.23,24 By age 1 year, the infant has learned to respond to his name and has started to repeat some speech sounds and to point to what he wants. He has discovered the power of communication and understands the meaning of the tone of voice of his caretaker. The infant has spent a lot of time practicing babbling in his crib and utters his first meaningful word at about 1 year of age. By age 18 months, his vocabulary has increased to anywhere from a dozen to 50 words. by age 2 years the infant has started to put two meaningful words together into short phrases, and by age 3 years he has acquired the main rules of grammar and speaks in full sentences. Progress thereafter consists of mastering an ever-increasing vocabulary and refining the rules of grammar to permit the comprehension and production of highly complex sentences and ideas

When should the physician be concerned about a child's language acquisition (Table 4)? Any infant who does not engage in responsive cooing and babbling, who has not learned to point to what he wants at about 1 year of age, who does not have a vocabulary of at least ten meaningful words by age 18 months, who has not started to use meaningful phrases by age 24 months, whose speech is unintelligible out of context to his parents at age 2 years and to strangers at 3 years, who does not use language communicatively and talks to himself rather than to express wants or comment on what is happening, and who does not understand what his parents say to him is at risk. Any of these complaints should trigger investigation and usually referral for intervention (see part 2 of this article).

Classification of Dysphasia

There is no universally agreed on classification of developmental dysphasia, although the consensus today is that there is more than one type of dysphasia. 18,25 Allen and Rapin^{11,12,26} have hypothesized the existence of at least six variants, based on clinical evaluation of the child's conversational language during play (Table 5). This

Table 5.—Dysphasic Syndromes According to Allen and Rapin et al1.11.12.26

Expressive disorders with normal comprehension

Verbal dyspraxia (mute or very dysfluent, speech articulation severely impaired)
Speech programming disorder (fluent but very poor speech articulation)
Mixed disorders with impaired articulation

Verbal auditory agnosia or word deafness (understand little or nothing, mute or very dysfluent with severely impaired articulation)

Phonologic-syntactic syndrome or mixed receptive-expressive disorder (comprehension impaired but better than production, speak in short incomplete sentences with impaired articulation)

Higher-order processing disorders (with adequate articulation)

Lexical-syntactic disorder (spontaneous language better than elicited speech, syntax immature rather than deviant, word finding deficit in discourse)

Semantic-pragmatic disorder (verbose, impaired conversational use of language and comprehension of discourse, perseveration, delayed and immediate echolalia frequent, no syntactic deficit)

classification is based on an inputprocessing-output view of the language system and on consideration of disorders at the levels of phonology (rules governing the comprehension and production of speech sounds), syntax (rules for assembling words into well-formed sentences), semantics (rules for selecting words from appropriate categories so as to convey meaningful messages), and pragmatics (rules for engaging in conversation, initiating communication, requesting information, commenting, etc).

Unless specifically interested, pediatricians need not be intimately familiar with these or any other hypothesized syndromes. They are provided here to illustrate the current state of the art in clinical subtyping. My colleagues and I are involved in a multidisciplinary project attempting to develop validated subtyping of dysphasic children useful to professionals from all the disciplines concerned with their diagnosis and management.

Diagnosis

The role of the physician is to identify as early as possible children whose language development lags behind expectation and to refer them for evaluation of their hearing, language, and cognitive skills (see part 2 of this article). It is also the physician's responsibility to try to determine the etiology of the disorder and to refer the child to an appropriate remedial setting.

Prognosis

With the exception of the most severely affected children with verbal dyspraxia and verbal auditory agnosia (Table 5), the majority of dysphasic

children learn to speak adequately by school age. This does not mean that they are no longer language impaired because many of them will have difficulty learning to read, spell, and express themselves in writing. It remains for future research to determine whether there are specific types of preschool dysphasia that herald particular types of learning disabilities.

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Book Review

Your Child's Health: A Pediatric Guide for Parents, by Barton D. Schmitt, \$12.95, New York, Bantam Books Inc, 1987.

Pediatricians know that being a parent is a hard job. Parents get plenty of well-meaning advice along the way, but sifting through it all and knowing whom to believe may leave them feeling confused and beleaguered. Your Child's Health, by Barton Schmitt, is a book that parents will really find helpful. Dr Schmitt has brought his considerable experience in general pediatrics to the writing of a text that is clear and well organized and that emphasizes both preventive care and common sense.

The book is divided into five major sections that cover emergencies, trauma, newborn care, behavioral problems, and common illnesses. There is also a brief glossary of medical conditions that require physician input for diagnosis and/or treatment. These are mentioned by medical name (eg, amblyopia and epiglottitis), and then explained in clear terms that can be understood easily by

Dr Schmitt has carefully avoided using complex medical terminology or jargon in the main sections of the book, making it refreshingly easy to read. His style is authoritative but not intimidating.

Topics are organized alphabetically ("Breathing Difficulty," "Burns," "Coma," "Convulsions," "Delirium," etc) for easy reference. Each topic has an explanation of the problem, clear instructions for first aid or home care, guidelines that describe when it is appropriate to call the child's physician immediately and when parents should call later, usually during office hours. When appropriate, preventive measures are discussed so that the problem can be avoided in the future. Explanations are clear, thorough, and full of common sense.

Dr Schmitt has made an effort to trim topics to their bare essentials in the "Emergencies" section, to make clear what must be done immediately and what can safely be deferred. However, in recommending this book to parents, I suggest that they read the section on emergencies at least once, preferably more than once, before an emergency arises. I tried to imagine reading about some of the emergencies as if I were a frightened and distraught parent whose child had just been found after an ingestion or a seizure with fever. Even the brief two or three pages that I had to read seemed overwhelming. For acute situations, it might be a good idea to suggest that a family member or neighbor read the appropriate section aloud while the parent stayed with the child and followed the advice, if this were possible.

The section on behavioral disorders deserves special mention. In his introduction, Dr Schmitt states to parents: "The . . . behavior of childhood will come into perspective as something you can competently manage. Don't underestimate your abilities." His discussion of behavioral problems in children and their management tries to give parents specific child-rearing techniques with which to work. The problems discussed are, by and large, common. Dr Schmitt begins each discussion with a guiding rule or principle for parents to teach their children. (For example: "Don't fight with each other, because disagreements can't be settled by hitting.") A discipline technique is then suggested. Emphasis is placed on clear, firm, limit-setting with logical consequences and use of time-out, not physical punishment. The time-out technique is taught clearly. Parents are encouraged to look for opportunities to praise a child when he or she is behaving appropriately and are taught to use their own behavior as a model for their children. For example, when discussing aggressive behavior in children, Dr Schmitt suggests the following parental model: "Self-control and verbal problem-solving. Don't use physical punishment to try to change aggressive behavior. For example, don't bite back, because it teaches your child it's fine to bite if you are bigger." One of the things I like best about this section is that it is full of "dos," things that parents can do to take control of a situation, and not just "don'ts," which may leave parents wondering what they are supposed to do.

Although the same format is used throughout the book, the section on newborn care discusses questions in a slightly more conversational style, imparting more information to parents. Common questions about breast- and formula-feeding, crying, diet, sleep, and accident prevention are discussed, as are common problems such as diaper rash and spitting up and problems with the umbilical cord. Other medical problems and problems beyond the newborn period are organized by organ system, for easy reference. Although practitioners of pediatrics may have slight variations in style or recommendations (eg, a favorite dietary regimen for children recovering from diarrhea), Dr Schmitt's advice is generally sensible, practical, and widely accepted medical practice. It was reviewed by a board of 11 pediatricians and seven parents. Dr Schmitt's writing style is comfortable, and after using the book for a while, parents may feel that he has become a family friend and trusted adviser.

Your Child's Health is a book to which parents will refer over and over again. It is a carefully thought-out text that will be read by parents with gratitude to Dr Schmitt for writing it and to you for recommending it.

BETSY BUSCH, MD Department of Pediatrics Boston Floating Hospital New England Medical Center Boston, MA 02111

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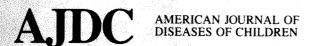


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Continued from p 1126.

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Kazimierz Kozlowski, MD,

Edward H. Bates, MD (Contributors), Sydney, Australia; Lionel W. Young, MD (Editor for This Case), Akron, Ohio; Beverly P. Wood, MD (Section Editor), Rochester, NY

1235 Radiological Case of the Month

Bruce A. Schroeder, MD; David J. Czarnecki, MD; Robert G. Wells, MD; John R. Sty, MD (*Contributors*), Milwaukee; Lionel W. Young, MD (*Editor for This Case*), Akron, Ohio; Beverly P. Wood, MD (*Section Editor*), Rochester, NY

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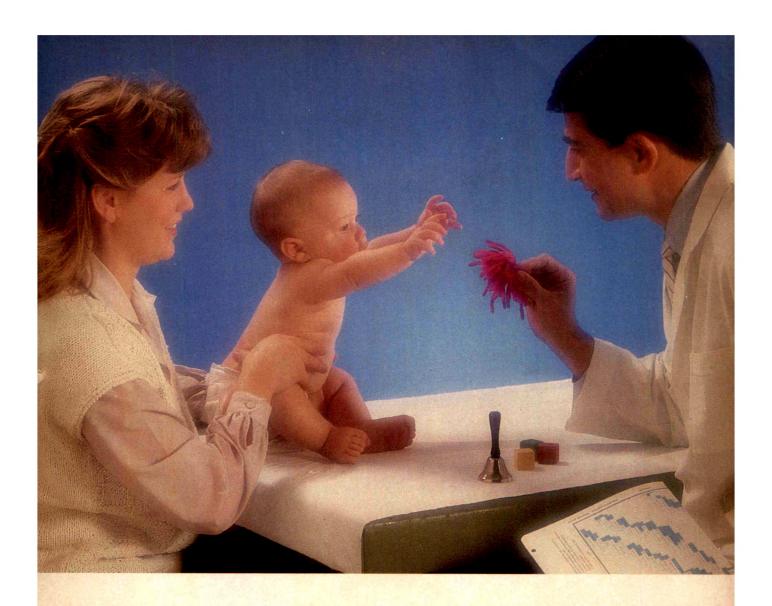
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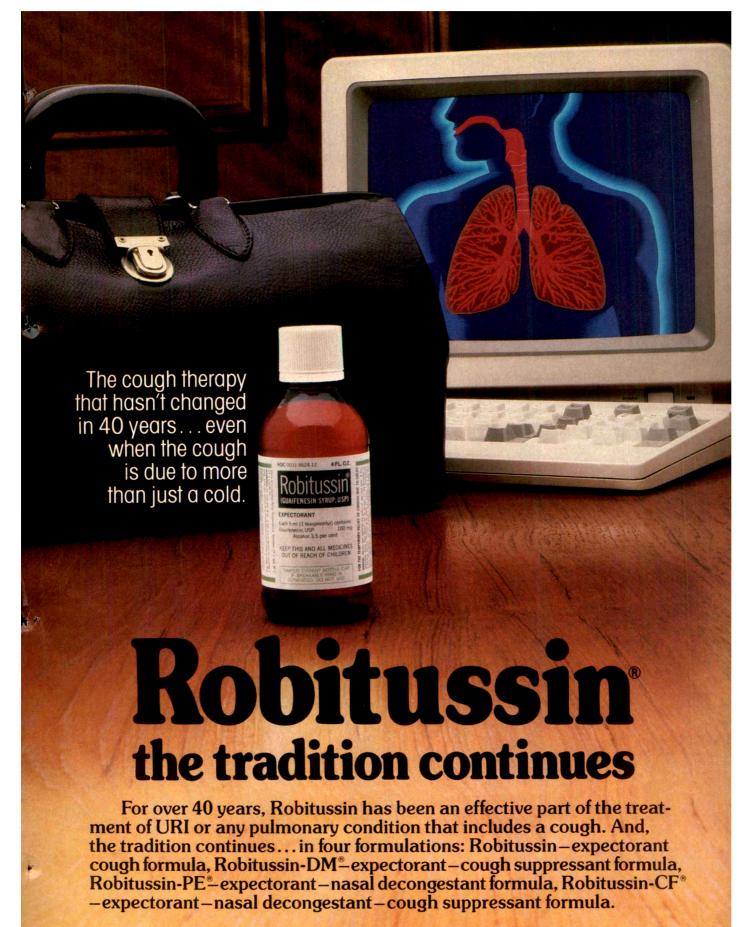
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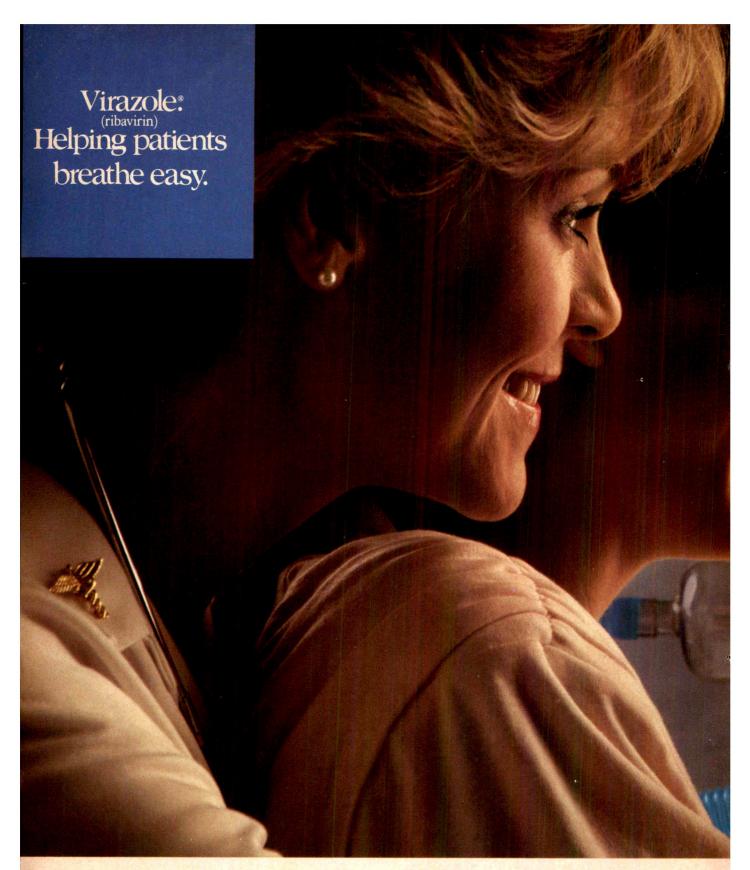
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nake positive diagnosis possible in less than 30 minutes. And inical evidence and experience continue to confirm that early nitiation of Virazole therapy provides more rapid clinical mprovement and may shorten hospitalization.²⁻⁵ or complete prescribing information, please see next page.

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VIRAZOLE® (ribavirin) aerosol is indicated for treatment of severe lower respiratory tract infections due to RSV in carefully selected, hospitalized infants and young children.

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has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring ous monitoring.
Although ribavirin is not indicated in

adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

DESCRIPTION:

DESCRIPTION:

Virazole *{ribavirin} Aerosol. an antiviral drug. is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 mi glass vial contains 6 grams of ribavirin. and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin. pl approximately 5.5. Aerosolization is to be carried out in a SPAC-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1.2.4-triazole-3-carboxamide, with the following structural formula:

structural formula



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is C₈H₁₂N₄O₅ and the molecular weight is 244.2 Daltons.

CLINICAL PHARMACOLOGY: Antiviral effects:

Ribavirin has antiviral inhibitory activity in vitro against respiratory syncytial virus. influenza virus, and herpes simplex virus.

influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats. In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the in ultro antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Immunologic effects:

mmunologic effects:
Neutralizing antibody responses to RSV
were decreased in ribavirin treated compared to placebo treated infants. The clinical
significance of this observation is unknown.
In rats. ribavirin resulted in lymphoid
atrophy of thymus, spleen, and lymph nodes.
Humoral immunity was reduced in guinea
pigs and ferrets. Cellular immunity was also
mildly depressed in animal studies.

Microbiology:

Several clinical isolates of RSV were evalu-Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16µg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects riba-virin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol adminis3 days had plasma concentrations ranging from 0.44 to $1.55\,\mu\text{M}$, with a mean concentration of $0.76\,\mu\text{M}$. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to $14.3\,\mu\text{M}$, with a mean concentration of $6.8\,\mu\text{M}$. It is likely that the concentration of ribavirin in respiratory tract secretions is much

virin in respiratory tract secretions is much

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations. In man, rats, and rhesus monkeys, accumulation of ribavirin andor metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

INDICATIONS AND USAGE:

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytal virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 30 severity of clinical manifestations of disease. 3.4 Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies. 4. Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract

nospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection. The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of

been evaluated in only a small number of

been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace stan-dard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

RSV infection should be documented by a rapid diagnostic methods uch as demonstration of viral antigen in respiratory tract secretions by immunofluorescence 3 or teatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection. RSV infection should be documented by a

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this contrained. Ribaviris is not completely population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:
Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days.

to human administration is unknown. Ribavirin lyophilized in 6 gram vials is intended for use as an acrosol only.

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs meractions of noavine with other artigs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or antimetabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an in vitro mammalian system (Balb/C 3T3 cell line). However, in vivo carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

adrenal tumors.
Ribavirin is mutagenic to mammalian (LSi78Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay imouse) were negative.
Ribavirin causes testicular lesions tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated adequately investigated.

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.
Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to locatating animals and their offspring. It is not known whether the drug is excreted in human milk.

ADVERSE REACTIONS:

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Severalseriousadverseeventsoccurredin severely ill infants with life-threatening underlying diseases. many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

<u>Pulmonary:</u> Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

was attributed to fibavinin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation offluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been asso-

aerosoi use.
Rash and conjunctivitis have been asso-ciated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD₃₀ in mice is 2 gm orall Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is seques tered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION:

Before use, read thoroughly the Viratek Small Particle Acrosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle acrosol generator operating instructions.

istructions. Treatment was effective when instituted Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.³ Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours perday for at least 3 and no more than 7 days, and is part of a total treatment program. The account is delivered to an infant over the normal course of the sevent is delivered to an infant over the normal course of the sevent is delivered to an infant over the normal course of the sevent is delivered to an infant over the normal course of the sevent had a sevent in the sevent in the

from the SPAC-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosols should not be used for patients.

other aerosol generating device or together with other aerosolized medications. Ribavirin aerosolshould not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml widemouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. Important: This water should not have had any antimicrobial agent or other substance added. The solutions should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/ liter (0.19 mg/l) of air.

HOW SUPPLIED:

HOW SUPPLIED:

Virazole® (ribavirin) Aerosol is supplied in 100 mi glass vials with 6 grams of sterile. Iyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the Iyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hour

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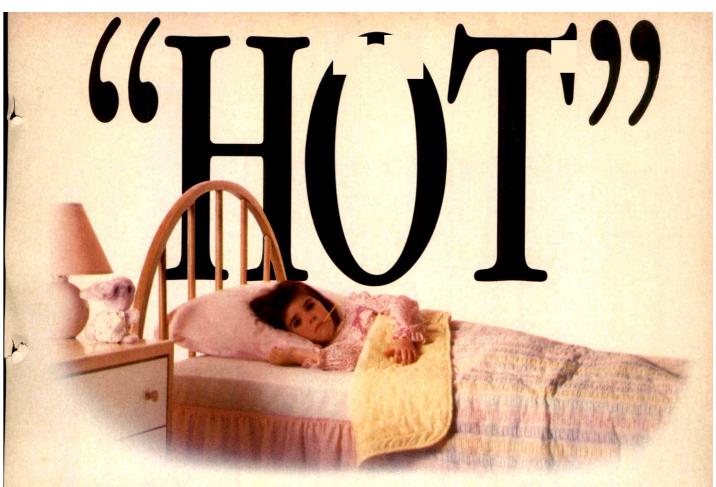
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Kawasaki Disease With an Exanthem Limited to the Diaper Area

Sir.—The occurrence of a rash, usually described as truncal, is one of the major criteria for the diagnosis of Kawasaki disease. 1 The exanthem may appear morbilliform or scarlatiniform or may be composed of erythematous plaques or papules, thereby simulating urticaria or erythema multiforme.1,2 Less frequently, vesicles, pustules, or petechiae may be observed.1 Recently, three groups of investigators have described patients with Kawasaki disease in whom the exanthem either began or was most prominent in the diaper area.2-4 We report a 21-month-old child with Kawasaki disease whose only acute cutaneous manifestation was an exanthem limited entirely to the diaper area.

Patient Report.—A 21-month-old male child developed fever (maximum temperature, 40.7°C), rhinorrhea, dry cough, and occasional vomiting six days prior to admission. Two days prior to admission, he was noted to have a decrease in activity, anorexia, and a diaper rash. The fever and reduced level of activity persisted, and on the day of admission he was evaluated in the Pediatric Clinic at Cleveland Metropolitan General Hospital. The child's medical history was unremarkable and prior testing for sickle cell disease had yielded negative results.

The physical examination revealed a moderately ill-appearing, quiet, alert child. Remarkable aspects of the examination included a temperature of 40.7°C, bilateral conjunctival hyperemia without discharge, an erythematous pharynx without exudates, an equivocal strawberry tongue, otitis media, and mild enlargement of the anterior cervical and inguinal lymph nodes (maximal node diameter, 1 cm). Examination of the diaper area (Figure) revealed dusky erythema of the suprapubic region and medial proximal thighs. There was erythema and desquamation of the scrotum and penis. A Nikolsky sign was not elicited. The fingers, although nonerythematous, appeared minimally edematous. Examination of the heart and lungs was normal.

Initial laboratory studies included a complete blood cell count, with a white blood cell count of 17.7×10°/L, 6.51 segmented neutrophils, 0.21 band neutrophils; hemoglobin, 90 g/L; and hematocrit, 0.26. The platelet count was 682×10°/L, reaching a maximum of 881×10°/L on the third hospital day. The erythrocyte sedimentation rate was 114 mm/h. A chest roentgenogram revealed a confluent right middle lobe infiltrate. The electrocardiogram demonstrated sinus tachycardia without evidence of acute myocardial injury. Electrolyte levels, liver function study, urinalysis results, and blood culture were normal.

A presumptive diagnosis of Kawasaki disease was made, and treatment with intravenous gamma globulin (400 mg/kg/d) and aspirin (100 mg/kg/d) was initiated. Within 24 hours, the child's fever had resolved and conjunctival hyperemia had diminished. By the third hospital day (day 8 of the illness), the child appeared clinically well. His exanthem was much less erythematous and exhibited peeling at its margins. An echocardiogram demonstrated a 4-mm right coronary artery aneurysm. The child remained clinically asymptomatic as he completed a five-day course of intravenous gamma globulin. He was discharged

home while receiving low-dose aspirin therapy (5 mg/kg/d). At follow-up, four days following discharge (13 days following the onset of illness), the child manifested peeling of the fingers and, to a lesser extent, the toes. Presently, the child is asymptomatic, and a repeated echocardiogram, performed two months following the onset of illness, demonstrated complete resolution of the previously noted aneurysm.

Comment.—The occurrence of a perineal rash in Kawasaki disease was first described by Fink³ in 1983. In his report of two cases, the exanthem was most prominent in, but not limited to, the perineum. In a subsequent case series, Aballi and Bisken4 observed that the diaper area was the initial site of exanthematous involvement in 25 of 40 patients with Kawasaki disease. It is not apparent from their communication, however, whether the exanthem was limited to this site. Of the two additional cases reported by McCuaig and Moroz,² one appears to have manifested an eruption limited to the diaper area.

The patient with Kawasaki disease

Diaper area demonstrating dusky erythema of suprapubic region and medial proximal thighs. Patient also exhibits erythema and peeling of scrotum and penis.



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described herein exhibited an exanthem that was highly unusual because of its limitation to the diaper area. The presence of a "diaper rash" in an infant or child with prolonged fever might initially suggest a diagnosis of incidental candidiasis, seborrheic dermatitis, or irritant dermatitis. However, the type of erythema, prominent desquamation, and cutaneous edema mimicking lichenification were atypical of and inconsistent with these conditions. Other differential diagnoses included scarlatiniform eruptions produced by streptococcal or staphylococcal infections, staphylococcal scalded skin syndrome, toxic epidermal necrolysis, and drug allergy. We believe that it is highly important to know that the exanthem of Kawasaki disease may be confined to the diaper area. Recognition of this finding as a manifestation of the overall systemic process may prevent delays in diagnosis and the institution of appropriate therapy.

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The authors thank Cutter Biologicals, West Haven, Conn, for financial assistance with the color reproduction.

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French Screening Programs for Congenital Hypothyroidism

Sir—We were interested in the article by Allen et al1 in the February 1988 issue of AJDC about neonatal screening for congenital hypothyroidism (CH) because their strategy is totally different from ours. Some of the modifications they proposed to improve CH screening are already included in the French program in respect to the organization model that was chosen ten years ago.2 In each region, the same team (pediatricians and bio-

chemists) is responsible for the screening and the follow-up.

The area covered by our center represents 79 000 infants born each year in the Nord Pas-de-Calais region (in northern France), which is similar in size to that of Wisconsin and allows the following comparisons.

Patients and Methods.—Infants undergo filter paper thyrotropin (TSH) testing on day 5 of life. Those with a TSH level higher than 30 mU/L are retested for TSH (in duplicate) on the same sample. A TSH level still higher than 50 mU/L is reported as "abnormal" and the family physician receives a telephone call to help the family to understand the need to refer the child as soon as possible to the specialized outpatient clinic for complementary investigations. A TSH level between 30 mU/L and 50 mU/L is "possibly abnormal" and a second specimen is taken.

Clinical examination, roentgenographic evaluation of bone maturity, blood (TSH, thyroxine [T₄], free T₄, thyroxine-binding globulin) and urine (ioduria) collection, and an iodine 123 scan are performed. According to the results, treatment is begun immediately, using a solution of levothyroxine with dose adaptation to keep the TSH level below 7 mU/L and the T4 level within the normal range. The follow-up of patients undergoing treatment consists of monthly filter paper TSH measurements, a quarterly serum hormone and clinical evaluation, and a yearly roentgenographic and psychometric evaluation. The entire followup procedure is reviewed by the same pediatrician.

Results.-With an initial sampling of blood on day 5 of life, the incidence of positive tests (controlled TSH value above 30 mU/L in the initial sample) was 0.2%; in this group, 79% of recheck on the same sample have normal TSH levels (false-positive or transient TSH elevation). Among children undergoing confirmatory investigation, only two or three a year (of 20) are true false-positives. Causative distribution is 69.6% ectopic glands, 20.7% athyrosis, and 9.9% normally located glands. All the infants with a TSH higher than 50 mU/L in the initial samples have been referred, and hypothyroid patients were treated before five weeks of life (mean ± SD, $20.6 \pm 5.9 \text{ days}$).

Thyroxine levels usually returned to the normal range within the first three weeks of treatment.

Comments.—Our strategy is totally different from that in the United States because a centralized organization exists for both screening and follow-up procedures. Consequently, 100% of CH suspected by the screening are referred to the clinic. In addi-

tion, the French Association collects information on screening results and can provide updated guidelines to the regional centers.

Despite the principle of liberal medicine, the centralization has never introduced conflicting relations with family physicians or other pediatricians. On the contrary, a tacit consent exists that agrees with the need of centralized centers for the diagnosis and follow-up of rare diseases such as CH cases and phenylketonuria. However, it has to be emphasized that the family physician still has a key role in continuing to help the family to manage the disease. He or she is informed from the center of all the results of the follow-up.

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In Reply.—Farriaux and Dhondt describe a centralized screening program for CH based on detection of elevated serum concentrations of TSH and suppression of TSH during treatment. I wish to note some merits and weaknesses of this approach vis-à-vis the primary T₄-supplemental TSH measurement and treatment strategy described in our article.

With either strategy, some infants with CH will be missed. Primary TSH testing does not detect thyrotropinreleasing hormone or TSH deficiency, or late-onset TSH elevations.1 On the other hand, LaFranchi et al² reported that, using a primary T₄-supplemental TSH approach, approximately 10% of infants with primary hypothyroidism were not detected until a second screen was performed at 4 to 6 weeks of age. Virtually all of these infants had detectable thyroid tissue at the time of diagnosis, and half had low TSH concentrations on the first screening specimen that would not have been detected by a primary TSH screening program.2 Our experience indicates a much lower false-negative rate; nevertheless, failure to detect compensated hypothyroidism (ie, normal T4 with an elevated TSH) can occur using a primary T₄-supplemental TSH approach. Primary T₄-supplemental TSH measurement remains the predominant screening approach in the United States.

I caution against suppression of TSH levels to below 7 mU/L as a therapeutic goal for CH during infancy. In some infants who appear to have a disorder of TSH control (ie, decreased pituitary sensitivity for TSH suppression by T, or triiodothyronine), elevation of serum TSH concentrations remain despite adequate treatment. Thyroxine supplementation given in amounts necessary to suppress TSH to the normal range can result in hyperthyroidism,1 accelerated growth, and advancement of bone age.

Our report demonstrates the high frequency of false-positive tests that result from testing within the first 36 hours of life. An initial sampling at 5 days of age, advocated in the letter above, would dramatically decrease the number of false-positive tests. But how is compliance with universal newborn screening assured if tests are obtained after discharge from the nursery? And who, physician or parent, is legally responsible for obtaining a blood sample from the infant who does not return at 5 days of age? These are questions confronting screening programs as the trend toward earlier discharge from the newborn nursery continues.

We agree that "tacit consent" should exist regarding the need for centralized follow-up of rare diseases. The dramatic success of newborn thyroid screening is testimony to cooperation between family physician and consultant in the diagnosis of CH. Our survey indicates, however, that a previously unnoticed "spirit of independence" can be found in many primary care physicians when it comes to treatment and follow-up of these children.

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Decreasing Frequency of Diabetic Nephropathy

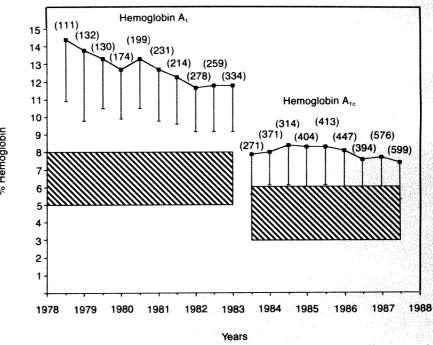
Sir.—The frequency of diabetic nephropathy appears to be decreasing. Studies of the incidence of diabetic microvascular disease from the early 1950s and 1960s indicated that about 50% of patients with insulin-dependent diabetes would develop renal disease after ten to 30 years of diabetes. 1-3 More recent studies indicate that the percent of patients developing renal failure is about 35%. Kofoed-Enevoldsen et al4 and Krolewski et al5 indicate that both hyperglycemia and individual susceptibility play a role in the development of diabetic renal disease. Thus, patients with higher blood glucose levels are more likely to develop this complication of diabetes.

The quantitation of the severity of hyperglycemia has only been possible in the last ten years with the advent of the measurement of glycosylated hemoglobin and the feasibility of monitoring blood glucose levels throughout the day at home. We have been measuring the former since July 1979 and using the latter routinely for all patients since 1980. It has been our impression that blood glucose control as determined by glycosylated hemoglobin measurements has improved over the course of years. Thus, we reviewed all measurements of hemoglobin A, (Bio-Rad Laboratories,

Richmond, Calif) and hemoglobin A_{1e} (Bio-Rad Laboratories, Richmond, Calif) performed in our laboratory, as previously described,6 from the beginning of its use to the present.

The patients are children with insulin-dependent diabetes mellitus followed up at the Children's Diabetes Management Center, The University of Texas Medical Branch, Galveston. They are routinely seen in the clinic every four to six months, with glycosylated hemoglobin samples being drawn at the time of the visit. The Figure shows all glycosylated hemoglobin measurements (mean ± SD) at six-month intervals. During the first six months of 1983, we changed from measuring hemoglobin A, to measuring A_{1c}; because both measures were used during this time, we deleted this period from the data presented herein. It is clear that the percent of glycosylated hemoglobin has decreased since 1979, indicating overall better blood glucose control. The cause of the improvement in this measure of blood glucose control is not clear; the majority of our patients continue to receive two daily injections of insulin as they did in 1979 when we first introduced the measurement of glycosylated hemoglobin, and the percent of patients using the subcutaneous insulin infusion pump has remained about 10% to 12%.

Mean (±SD) glycosylated hemoglobin measurements in children with type I diabetes measured for nine years. Total number of determinations are indicated in parentheses. Home blood glucose monitoring was routinely performed by all patients beginning in 1980. Nondiabetic control values are noted in shaded areas.



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These data suggest that one of the significant factors associated with the development of diabetic nephropathy. namely, hyperglycemia, may not be as prevalent as it was ten years ago; thus, the likelihood of development of nephropathy for children developing diabetes today is less than it was ten to 15 years ago.

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The Role of Imaging in Neonatal Hypothyroidism

Sin-We read with much interest the report on congenital transient hypothyroidism and the role of transplacental thyrotropin (TSH)-blocking antibodies that appeared in the October 1987 issue of AJDC. Drs Francis and Riley are to be commended for their clear presentation of a rapidly evolving clinical topic, which has attracted the attention of physicians from such diverse specialities as pediatrics, endocrinology, clinical pathology, immunology, and diagnostic imaging. As practitioners of three of these specialties, we found the review comprehensive and informative but we disagree with their view that "the thyroid scan is of limited value in evaluation of transient neonatal hypothyroidism." We routinely image the neck sonographically to distinguish athyreosis from other forms of congenital hypothyroidism. In the absence of sonographically visible thyroid tissue in the neck, a technetium scan will clearly localize an ectopic gland. With tissue visualized on sonogram, the scintigram will distinguish an enzyme defect from TSH-blocking antibodies as the cause of low serum thyroid

hormone levels. The typical situation is not that encountered by Drs Francis and Riley in which the mother was known to have autoimmune thyroid disease and elevated TSH-blocking antibodies. The usual case involves a neonate found on screening to have low thyroxine and elevated TSH levels. In such a situation, the diagnosis of ectopic thyroid, athyreosis, and/or dyshormonogenesis defect can be rapidly established by sonography and, if necessary, technetium scintigraphy.

The nuclear study is indicated to (1) confirm the thyroidal origin of a lingual mass found on physical examination or other neck mass identified by ultrasound, (2) search for an ectopic site when the sonography fails to visualize the gland, and (3) distinguish dyshormonogenesis from TSH-blocking antibodies or iodine-induced goiter as the cause of inadequate production of hormone.

As a final consideration, in transient forms of hypothyroidism, the decision as to when to discontinue treatment is highly controversial. We believe that the technetium scintigram is an accurate indicator of thyroid function in infants with transient hypothyroidism. We are currently treating a patient for low neonatal thyroid hormone levels associated with TSH-blocking antibodies. His thyroid hormone need is dropping, and we plan to use a repeated nuclear study as another marker of thyroid function.

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Invalid Equation for Conversion of Indirect Hemagglutination Titers to International Units

Sir.—While reading the article by Anderson et al,1 we noticed that the indirect hemagglutination (IHA) values were converted to international units (IUs) by using an equation that, we assume, based on their reference 24, was the one derived at the Institutes of Laboratories, Massachusetts Department of Public Health, Boston. Our experience with this equation may be important.

In the 1960s, while under contract to the National Communicable Disease Center, we studied the serologic responses to the antigens in the available diphtheria-tetanus-pertussis vaccine. For practical reasons, the IHA technique was also chosen to determine the response to both tetanus and diphtheria toxoids on all samples. The procedures for the IHA tests for both tetanus and diphtheria, as standardized at the Institutes of Laboratories, were followed using the Institutes' purified toxoids. Conversion of IHA titers to IUs was carried out using its equation. We sought confirmation mouse neutralization antibody levels to tetanus on selected sera. To our dismay, no neutralizing antibody level could be determined on the first sample tested after screening at numerous levels that bracketed the "converted IU value.'

Therefore, we requested and received the original data from the Institutes of Laboratories. It was determined that the equation was based on the "log of the log" of the IHA dilutions and that the curve obtained with the log values was S-shaped. This finding was reported to the late Geoffrey Edsall.

Surján and Nyerges,23 at the State Institute of Hygiene in Budapest, and Scheibel et al,4 at the Statens Seruminstitut in Copenhagen, carried out comparative studies and found a poor correlation of the IHA and biological titrations at both low and high antibody levels, with close correlation within the linear portion of the curve only when sera of similar avidity were compared. Since the "avidity phenomenon"5.6 is recognized to affect results obtained on sera that contain antibodies of different binding strength, we must conclude, based on previous data, that valid comparisons cannot be made from results obtained with nonbiological assays, such as the IHA, using sera obtained around the time of priming doses of antigen and obtained immediately before or following secondary or booster doses.

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In Reply.—We wish to respond to the letter from Drs Wilkins and Wehrle concerning our previous publication. We agree that toxin neutralization (TN) tests are superior, in principle, to IHA tests for determining neutralizing antibody titers, because the latter may be responsive to antibodies that bind toxin without neutralizing it. For this reason, we used a tissue culture TN test to assay antibody titers against diphtheria toxin. However, no such assay was available for antibodies against tetanus toxin and, given the large number of sera to be evaluated, we preferred IHA to the alternative, the cumbersome mouse protection test. Contrary to the opinions cited by Drs Wilkins and Wehrle, we note that many researchers have found good correlation between the IHA and mouse tests for tetanus antitoxin titers, 1-6 including Dr Nyerges. Drs Wilkins and Wehrle cited two 1962 articles by Dr Nyerges (with Dr Surján) reporting a poor correlation between the two tests. In the later reference 6, Dr Nyerges found that using native rather than fixed erythrocytes produced good agreement between the two methods. (We used native erythrocytes.)

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Parent-Child Minimal Change Nephrotic Syndrome

Sir-The two articles on IgA nephropathy that appeared in AJDC expanded our knowledge of this disease.1.2 After reading these articles, we would like to expand the spectrum of another common pediatric renal disease, minimal change nephrotic syndrome. While familial forms of minimal change nephrotic syndrome are not uncommon, the parent-child occurrence of this disease is essentially nonexistent.

Familial forms of minimial change nephrotic syndrome occur almost exclusively among siblings, with an incidence of approximately 3.3%.34 However, in our review of the Englishlanguage literature over the last 25 years, we found only one case of a parent-child occurrence of minimal change nephrotic syndrome.3 In this instance the father had onset of nephrotic syndrome at age 7 years and responded to corticotropin therapy but later had a relapse. The daughter had biopsy-proved minimal change nephrotic syndrome at 2 years of age that was responsive to prednisone therapy. We present the only other case of parent-child minimal change nephrotic syndrome we are aware of.

Patient Reports.-The father was a 35year-old man in whom generalized edema and proteinuria developed at age 22 years. He underwent a renal biopsy; the findings were consistent with minimal change nephrotic syndrome, and prednisone treatment was started. He had a complete remission but relapsed when the treatment was tapered. He became steroid dependent and required 20 mg of prednisone every other day.

At this writing the daughter was 8 years 8 months old. She presented with generalized edema, proteinuria, hypoalbuminemia, and hyperlipidemia at age 8 years 2 months. The clinical presentation was consistent with minimal change nephrotic syndrome, and she received a two-month course of prednisone, with complete remission. The mother had no history of renal disease. There was no history of consanguinity. The only other child in the family is adopted. The daughter's first cousin, however, did have generalized edema and kidney disease at 1 year of age; the diagnosis and treatment are not known, and she was free of disease at this writing.

Comment.-The above comments remind us of the familial aspect of minimal change nephrotic syndrome. We hope these patient reports will expand the spectrum of minimal change nephrotic syndrome to include parent-child occurrences.

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Removing Cactus Spines

Sin-Having read the letter by Hennes¹ in the June 1988 issue of AJDC regarding removal of cactus spines, I wish to offer another remedy that was recommended to me some 20 years ago by a nun at the Mission of San Luis Obispo.

Simply, take some adhesive tape or some cellophane tape and place it over the area of cactus spines. Remove the tape, and the spines will easily come out too. The process is safe, is virtually painless, and may be repeated as needed.

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The opinions expressed are solely those of the author and do not reflect the official opinion of the US Navy or Department of Defense.

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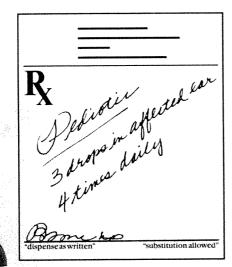
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HOW SUPPLIED: Bottle of 7.5 ml with sterilized dropper. NDC 0081-0910-02. Store at 15° to 25°C (59° to 77°F). REFERENCES: 1. Leyden JJ, Kligman AM: Contact dermatitis to neomycin sulfate. JAMA 1979;242: 1276-1278. 2. Prystowsky SD, Allen AM, Smith RW, et al: Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. Arch Dermatol 1979;115:959-962.

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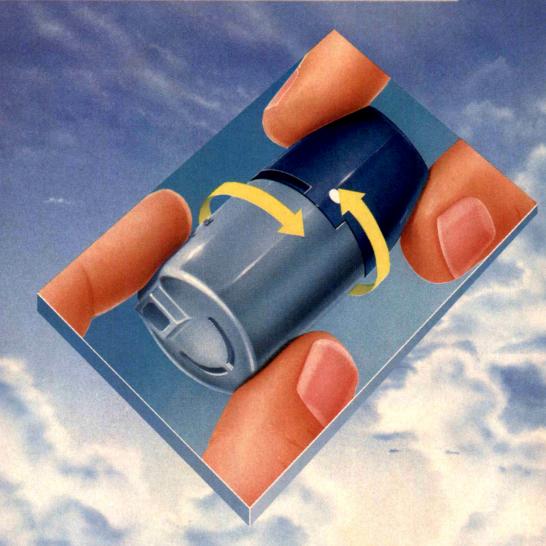
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Leads From the MMWR

Morbidity and Mortality Report Centers for Disease Control, Atlanta

Childhood Lead Poisoning—United States: Report to the Congress by the Agency for Toxic Substances and Disease Registry

INTRODUCTION

THE LONG-TERM consequences of unabated exposures to environmental lead sources can be serious, particularly for children. Recent scientific studies have shown a progressive decline in the lowest exposure levels of lead at which adverse effects can be reliably detected in children. In recognition of this, Congress directed the Agency for Toxic Substances and Disease Registry (ATSDR), in consultation with the Environmental Protection Agency (EPA), to examine the nature and extent of childhood lead poisoning in the United States. The study was to address such areas as the long-term health implications of environmental lead exposure in children, the extent of lead intoxication of children in terms of geographic areas and sources of lead in the United States, and methods and strategies for removing lead from the environment of U.S. children. This article summarizes the key findings of the report.1*

EXPOSURE CLASSIFICATION

The degree of exposure to children was classified by blood lead (Pb-B) levels of 25, 20, and 15 µg/dL. The groupings were based on 1) presence of both 25 µg/dL Pb-B and elevation of erythrocyte protoporphyrin (EP)**; 2) the corresponding value of 20 µg/dL used recently by the World Health Organization** for the European Economic Community; and 3) findings of EPA's Clean Air Scientific Advisory Committee,** which concluded that 10-15 $\mu g/dL$ of lead is associated with the onset of effects that "may be argued as becoming biomedically adverse".2 Levels of 25, 20, 15, and 10 µg/dL were used for grouping pregnant women and women of reproductive age when estimating fetal lead exposure and potential adverse health effects (2-4).

TOXIC EFFECTS OF LEAD

Infants and young children are at highest risk for the adverse health effects of lead.^{2,3} Exposures of women of childbearing age are also a concern because lead is directly transferred across the placenta; therefore, the developing fetus is exposed at levels proportional to maternal lead stores.⁵⁻⁷

The toxic effects of lead in children (Table 1) are evident across a broad range of exposures, and some occur at Pb-B levels previously considered noninjurious (i.e., less than $25~\mu g/dL$). Further follow-up studies are needed before the impact and persistence of the low-level neurobehavioral effects are fully known.

ESTIMATES OF THE NUMBERS OF CHILDREN EXPOSED TO LEAD

The only national data set for Pb-B levels in children comes from the National Health and Nutrition Examination Survey II (NHANES-II). Using this data set, ATSDR quantified the numbers of lead-exposed children (ages 6 months to 5 years) living in all SMSAs according to 30 socioeconomic and demographic strata and selected Pb-B levels.

These estimates for 1984 were projected from data collected in 1976-1980 (the years of NHANES-II). The degree of error in these estimates is difficult to quantify since sources of both overestimation and underestimation are present. In addition, Hispanic, Asian, and other subgroups are omitted because no data are available; however, no economic or racial subgrouping of children is exempt from the risk of sufficiently high Pb-B levels to cause adverse health effects.

For all SMSAs, about 400,000 fetuses are exposed to maternal Pb-B levels of more than 10 μ g/dL and are

therefore at risk for adverse health effects.

Of the estimated 2,380,600 children exposed to lead at levels above 15 μ g/dL (about 17% of the total 13,840,000 children within SMSAs), an estimated 715,500 (5.2%) and 199,700 (1.4%) children have Pb-B levels greater than 20 μ g/dL and greater than 25 μ g/dL, respectively.

ATSDR SURVEY OF LEAD SCREENING PROGRAMS

The most current data for lead screening results came from an ATSDR survey conducted in December 1986. All data for 1985 screening programs were voluntarily reported. There was no centrally administered data collection and assessment. Of 785,285 children screened by those programs in 1985, 11,739 (1.5%) had lead toxicity as determined by one of two CDC definitions (1978 criteria: a Pb-B level of 30 µg/dL and an EP level greater than or equal to 50 µg/dL; 1985 criteria: a Pb-B level 25 μg/dL and an EP level greater than or equal to $35 \mu g/dL$).

Based on examination of 1980 census data for children and their housing in the 318 SMSAs, for 35 SMSAs, greater than or equal to 50% of the children were at high risk of exposure to leaded paint because their housing was built before 1950. For all 318 SMSAs, 4.4 million children were at potential risk because they lived in older housing with high lead content paint.

SOURCES OF LEAD CONTRIBUTING TO HUMAN EXPOSURE

The ATSDR estimates of children exposed to lead by source are shown in Table 2. Because of the interrelating pathways of exposure, the numbers of children exposed to lead on a source-specific basis can only be estimated.

The total of approximately 12 million children exposed to leaded paint is for children less than 7 years of age; the estimated 5.9 million children in the oldest housing were less than 6 years of age. Of the estimated 1.8 to 2.0 million children living in old and deteriorated housing, approximately 230,000 would be expected to have Pb-B levels greater than 30 µg/dL and 1.3 million greater than 15 µg/dL because of leaded paint exposure.

The estimate of 5.6 million children less than 7 years of age potentially exposed to lead at some level from gasoline are derived for the number of children in the 100 largest urban areas in the United States where vehicular traffic could be expected to figure significantly in childhood lead exposure. This estimate takes into consideration the phase-down of lead in gasoline required by EPA regulations.

Although data are very limited, an estimated 233,000 children are exposed to lead from stationary sources of all types.⁸

Dust/soil lead is lead that has settled from leaded paint, gasoline, and stationary sources; therefore, exposure estimates can only be roughly calculated as the sum of these three categories. Dust/soil lead is the primary long-term repository for lead exposure; this pathway is a major contributor to overall lead exposure because of the hand-to-mouth activity of children.

Children are exposed to lead in drinking water primarily from contamination of the supply system (e.g., from lead pipes or from leachable lead solder). EPA recently estimated that 241,000 children less than 6 years of age have Pb-B levels greater than 15 µg/dL because of elevated concentrations of lead in drinking water, including 100 with Pb-B levels greater than 50 µg/dL, 11,000 with levels 30-50 µg/dL, and 230,000 with levels 15-30 µg/dL.9

REDUCING EXPOSURE TO LEAD

Primary environmental lead abatement has been most effective for gasoline, stationary lead sources, and food. Activities are now under way to bring significant reductions of lead in water. Despite the marked reductions of lead in new paint (in 1977, the

Consumer Product Safety Commission mandated the reduction of lead in paint to 0.06%), exposure to lead paint in old housing remains an important problem.

Abatement of secondary environmental lead exposure is closely linked to childhood lead-screening programs. These efforts involve environmental evaluation and abatement of exposure for children with recognized lead toxicity. Early screening and detection of exposure and toxicity have reduced the rates of severe lead poisoning. The success of screening programs in the past has been limited by the 1) difficulty of locating all children with lead toxicity; 2) inability to identify remediable sources of lead for many leadpoisoned children; and 3) incomplete removal of lead from the children's environments. Some methods of removing and disposing of lead from homes and other sites are relatively crude and can endanger both abatement workers and occupants.

REPORT RECOMMENDATIONS

Recommendations contained in the ATSDR report include the needs to 1) integrate comprehensive approaches to controlling lead exposure in high-risk areas of the United States, 2) establish and maintain effective and efficient screening programs, 3) develop environmental measurement techniques for field use, and 4) conduct research on childhood lead poisoning and develop effective legal sanctions.

Reported by: Agency for Toxic Substances and Disease Registry and Center for Environmental Health and Injury Control, CDC. (MMWR vol 37. No. 31).

CDC Editorial Note: Despite these reductions, childhood lead poisoning is not disappearing. The ATSDR lead report documents three critical developments in lead poisoning.1 First, long-term effects (particularly neurobehavioral, cognitive, and developmental) are increasingly being observed in studies of children with lead levels much lower than previously believed harmful. Second, the numbers of children exposed to lead at these new lower levels of concern (corresponding to Pb-B levels approximately greater than or equal to 15 µg/L) are estimated at several million. This estimate is largely based on projections from the data in NHANES-II; NHANES-III will provide updated data in the coming decade. Third, the remaining important sources of lead in the environment (primarily lead paint in older housing and lead in dust and soil from past deposition and from deteriorating housing) will be difficult and expensive to remedy.

Childhood lead poisoning is one of the most common environmental diseases of children in the United States. In concept, it is a totally preventable disease—remove the lead from the child's environment and the disease will disappear. In practice, eliminating childhood lead poisoning will require substantial commitment.

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^{*}The complete report is available on request from ATSDR, Mailstop F38, Atlanta, Georgia 30333.

**References are available on request from the Office of the Associate Administration, ATSDR, Mailstop F38, Atlanta, Georgia 30333.

The Editorial Board Speaks . . .

Denis R. Miller, MD





Denis is completing his ten-year stint as a member of the Editorial Board of AJDC. He has been a valuable contributor, reviewer, and board member. He has always provided timely advice to the Editor, has participated actively in our board meetings, and has responded to all requests for ideas, contributions, and expert analysis of articles. It is fitting that he marks his last months with us with his view on an emerging problem in pediatric oncology, since that has been the major area of his academic activity, and also his specialty role with the Editorial Board. All of us, but especially the Editor, wish to thank him for his competent and faithful service with, and for, AJDC.

LATE EFFECTS OF CHILDHOOD CANCER

Twenty-five years ago the outlook for children with cancer was poor. Fewer than 25% survived for three or more years. Rare exceptions to this grim experience included children with localized and totally resected Wilms' tumor and neuroblastoma and with stage I Hodgkin's disease, and the occasional patient with acute lymphoblastic leukemia (ALL). Major advances in diagnosis and treatment have increased cure rates to over 50% for all major childhood cancers except acute nonlymphoblastic leukemia, malignant brain tumors, and selected metastatic (stage IV) solid tumors. Major contributors to this success are the effective use of multimodality therapy, improved supportive care, and, more recently, the identification of clinical and biological prognostic factors that determine the relative intensity and duration of treatment.

It has been estimated that by 1990, 0.1% of all adults (1:1000) will be cured patients who had had pediatric cancer. Thus, physicians caring for children, adolescents, and young adults should be aware of the improved prognosis and the potential late effects of successful cancer therapy.

A constant goal of the pediatric oncologist has been to obviate or minimize the risks and hazards of therapy and, whenever possible, to ease the transition from being a child cured of cancer to becoming a well-adjusted adult capable of a full, productive life. Today this is difficult enough without the added burden of cancer and its aftermath. However, life must always be more than just survival. Truly effective therapy and true cure must be measured against the degree of long-term disability and disadvantage.

Late effects of cancer therapy can affect adversely every organ or system: cardiovascular, pulmonary, gastrointestinal, genitourinary, endocrine, gonadal, musculoskeletal, neuroendocrine, neuropsychological, hematopoietic, and immunologic. Perhaps the worst late effect of all is a second malignant neoplasm. Some secondary cancers have a genetic basis. For example, of nearly 100 children with retinoblastoma, 15% developed second malignant neoplasms, of which half were osteogenic sarcomas.

Enter another late effect of cancer therapy—malpractice litigation. Will oncologists be at risk for these rare occurrences? Other late effects were considered unavoidable ten years ago, but now we have learned that combined use of cranial irradiation and intrathecal chemoprophylaxis is associated with an unacceptably high frequency of neuro-

psychological disability, particularly when given to preschool children. Recent studies suggest that these late effects may be multifactorial, but to obviate them, most protocols today have deleted cranial irradiation in all children with ALL except those with the poorest prognosis. Is the pediatric hematologist at risk because a "cured" patient with ALL drops from a superior to an average range on the Weschler Intelligence Scale for Children? Other worrisome examples include leukoencephalopathy occurring as a late effect of high-dose intravenous methotrexate therapy, ALL occurring after replacement therapy with human growth hormone, and severe musculoskeletal deformities secondary to limb irradiation for Ewing's sarcoma.

Notwithstanding full disclosure of potential late effects, informed consent, well-known genetic associations of multiple tumor types, and legitimate concerns about potential adverse effects of therapy in patients with cancer, physicians and institutions are being charged with alleged negligence and deviation from accepted standard practice. The number of cases is small but their occurrence is alarming.

Curing childhood cancer has always been a challenging feature of pediatric oncology, and parent-physician and patient-physician relationships generally have been excellent. This is especially true when parents and patients are made key members of the multidisciplinary team. However, the litigation period of grace may be over. Merely curing children with cancer may no longer be adequate or reflect acceptable standards of care. Somehow, our challenge is to increase the rate of cure and diminish the frequency and severity of the late effects without compromising the good results achieved to date.

To meet these responsibilities, as pediatric oncologists, we must design more effective treatment protocols that minimize risk and maximize success (cure), avoid drug combinations and other modalities that increase these risks, develop innovative therapies that are more discriminating and less toxic in their anticancer effects, and communicate incisively and honestly with our patients and their parents about the benefits and risks of treatment. In effect, we need the proverbial magic bullet. Just when many of us were beginning to feel a real sense of accomplishment, a new medicolegal dimension has emerged.

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Campylobacter pylori-Associated Gastritis and Peptic Ulcer Disease in Children

Peter M. Kilbridge, MD; Beverly Barrett Dahms, MD; Steven J. Czinn, MD

 Specimens obtained at gastric biopsies performed for suspected acid peptic disease in patients 5 through 17 years of age were retrospectively reviewed for the presence of Campylobacter pylori (CP), a gram-negative bacillus associated with chronic gastritis and peptic ulcer disease in adults. Of 98 patients who underwent antral biopsy (the most reliably colonized site in the stomach), 40 had chronic gastritis histologically. Of those 40 patients, 22 (55%) had CP present on the gastric surface. None of the 58 patients without gastritis present in biopsy specimens had CP. The gastritis in children with CP was more severe than in those without the organism: 86% of those with moderate gastritis and 92% of those with severe gastritis had CP. Eight patients with duodenal ulcers and one patient with a gastric ulcer had CP on blopsy. Among those patients without CP, only one had a duodenal ulcer and eight had gastric ulcers. An additional nine patients found to have CP on gastric fundic biopsy were Identified, for a total of 31 patients with CP identified by either antral (22) or fundic (nine) biopsy. Initial resolution of symptoms with standard acid-antagonist therapy was noted in the 25 of 31 CP(+) patients so treated, but a high relapse rate was noted within one to two years in the patients who also had gastritis and duodenal ulcer. These findings support a strong association between CP colonization of the stomach and the presence of chronic gastritis and duodenal ulcer disease in children.

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Presented in part at the United States and Canadian Academy of Pathology, Washington, DC, Feb 29, 1988.

Reprint requests to Institute of Pathology, University Hospitals of Cleveland, 2085 Adelbert Rd, Cleveland, OH 44106 (Dr Dahms).

Since Warren and Marshall's report of spiral organisms in the gastric mucosa of patients with gastritis and the subsequent isolation and characterization of such organisms as Campylobacter pylori (CP), there have been many studies examining the association between CP, gastritis, and peptic ulcer disease in adults.²⁻⁶ Recently several studies have investigated the relationship between CP infection and primary gastritis in children.7,8 Using a large inventory of pediatric endoscopic biopsy material, we undertook in a retrospective study to investigate the prevalence of gastric CP in this patient population and to evaluate the association between the presence of CP and clinical presentation, endoscopic diagnosis, pathologic diagnosis, and response to traditional therapy.

MATERIALS AND METHODS

From 1979 to 1986, gastric biopsy specimens were obtained from 265 patients 5 to 17 years of age who underwent endoscopy for symptoms consistent with acid peptic disease such as chronic abdominal pain, vomiting, or hematemesis. Excluded from further analysis were patients with specific causes of gastritis such as eosinophilic gastroenteritis and chronic inflammatory bowel disease and also patients with previously established diagnoses such as leukemia and graft-vs-host disease.

Upper gastrointestinal tract endoscopies were performed using one of three commercially available endoscopes. Endoscopic findings were recorded at the time of the procedure. Gastric biopsy specimens were routinely fixed in Zenker's solution, embedded in paraffin, sectioned at a thickness of 4 to 5 μ m, and stained with hematoxylineosin (HE). In an effort to increase the sensitivity of screening for CP, Giemsa staining was also done in all cases in which CP was not visualized by HE. Giemsa stain has been shown to be particularly effective

for demonstrating CP, although HE is adequate in most cases. All HE-stained slides from gastric biopsy specimens were reviewed by two independent observers. The type of mucosa (antrum vs fundus) was noted. The degree of gastritis was assessed as mild, moderate, or severe and the quality of inflammation was graded as acute, chronic, or mixed according to standard criteria. Campylobacter pylori were sought under high dry magnification (×400) in the superficial mucous coat overlying the surface epithelium and within the superficial portions of gastric pits.

Medical records from the patients whose biopsy specimens disclosed CP were reviewed for presenting complaint, endoscopic diagnosis, treatment, and follow-up. In addition, clinical information regarding presenting complaint and endoscopic diagnosis was available for 67 of the remaining patients.

RESULTS

Two hundred sixty-five patients between the ages of 5 and 17 years underwent gastric biopsies during the seven-year review period. Of these patients, 166 met the criteria for inclusion in the study. As CP is most reliably found in the antrum and is predominantly associated with antral gastritis, 6,10 the specimens that included antral mucosa were analyzed separately. Ninety-eight patients, 22 with CP and 76 without, had antral material available (Fig 1). The mean $(\pm 1 \, \mathrm{SD})$ age of the 76 patients without CP disclosed by antral biopsy was 11.5 (± 5.2) years and that of the 22 patients with CP was $11.7 (\pm 3.0)$ years. The presenting complaints of the 22 patients with CP disclosed by antral biopsy were abdominal pain in 20 (91%), vomiting in 12 (55%), and hematemesis in four (18%) (Table 1). On endoscopy (Table 2), 16 (73%) of the children with CP had gastritis, eight (36%) had duodenal ulcers, and one

| Table 1.—Clinical and Endoscopic Findings in Patients With Antral Biopsy | | | | | | | |
|---|-----|---------------------------------|----------|-------------------------------|--|--|--|
| | | No. (%) o | Patients | | | | |
| | Pre | eacter pylori esent = 22) | Ab | acter pylori sent = 67) | | | |
| Clinical presentation | 20 | (91) | 5.4 | (81) | | | |
| Abdominal pain Vomiting | | (55) | | (22) | | | |
| Hematemesis | | (18) | 10 | (15) | | | |
| Endoscopic diagnoses Normal | 2 | (9) | 10 | (15) | | | |
| Gastritis | 16 | (73) | 48 | (72) | | | |
| Gastric ulcer | 1 | (5) | 8 | (12) | | | |
| Duodenal ulcer | 8 | (36) | 1 | (2) | | | |

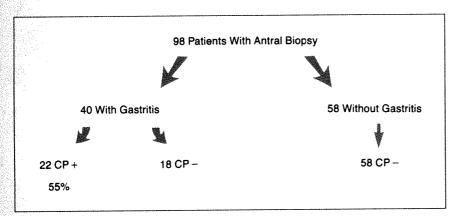


Fig 1.—Results of histopathologic examination in 98 patients in whom antral biopsy specimen was available for study. Of 40 patients with gastritis, 22 (55%) had *Campylobacter pylori* (CP) identified on antral biopsy.

(5%) had gastric ulcers; two patients had apparently normal mucosa. Of the 76 patients without CP, clinical information was available on 67. Fifty-four patients (81%) presented with abdominal pain, 15 (22%) presented with vomiting, and ten (15%) presented with hematemesis (Table 1). Endoscopic diagnoses included gastritis (48, or 72%), duodenal ulcer (one patient), and gastric ulcer (eight, or 12%) (Table 1).

Of the 98 children who underwent antral biopsy, 40 had histologic gastritis. All 22 of the patients with CP had histologic gastritis, constituting 55% of patients with antral gastritis. The presence of CP varied considerably with the severity of gastritis (Table 2). None of the 58 patients with histologically normal antral mucosa had CP. Of the 21 patients with mild antral gastritis, five (24%) had CP. However, six (86%) of seven patients with mod-

erate gastritis and 11 (92%) of 12 patients with severe gastritis had CP present.

Biopsy specimens from patients with antral gastritis were analyzed further to determine whether the gastritis was acute, chronic, or mixed. Of the 22 such patients with CP, four (18%) had chronic gastritis alone and 18 (82%) had mixed acute and chronic gastritis. None demonstrated acute gastritis alone. In most children with CP, chronic inflammation was dominant, with lymphocytes and plasma cells filling the lamina propria. Acute inflammation, although present in 82% of CP-positive patients, was nearly always focal and was usually limited to neutrophilic infiltration of occasional glands (Fig 2). In contrast, of the 18 patients with antral gastritis without CP, 13 (72%) had only chronic gastritis, four (22%) had mixed acute and chronic gastritis, and one had

| | .—Degree o | |
|---|-----------------------------|--|
| Degree of Gastritis | Total No. of Biopsies | No. (%) Positive for Campylobacter pylori |
| None Mild Moderate Severe Total | 58 21 7 12 98 | 0 (0) 5 (24) 6 (86) 11 (92) 22 |

acute gastritis alone.

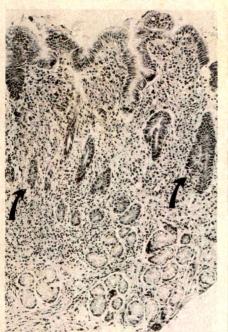
An additional nine patients with CP were identified among the patients who underwent fundic biopsy but not antral biopsy. Eight of these nine patients had histologic evidence of fundic gastritis; in the remaining patients, the fundus was histologically normal. Thus, a total of 31 patients had CP identified on gastric biopsy (22 antral and eight fundic biopsies).

Twenty-five of the 31 patients with CP were treated with standard acid (H₂)-antagonist therapy and were followed up (Fig 3). All of them had symptomatic improvement initially. Among the 15 patients with CP and endoscopic diagnosis of gastritis, nine had recurrent symptoms within two years and underwent biopsy again. Eight of these patients were found to have CP on the second biopsy, and three had developed duodenal or gastric ulcers. Follow-up endoscopy was performed on ten of 11 patients who had duodenal or gastric ulcers. Complete resolution of ulcers was seen initially in all cases. However, eight patients of the ten had recurrent symptoms within one year and on repeated biopsy CP was visualized in all eight of these patients.

COMMENT

Recent studies by Drumm et al^{7,8} in pediatric populations suggest that gastric CP is associated with primary antral gastritis and duodenal ulceration.⁷ The findings of the present large study provide further evidence for an association between CP and gastritis and peptic disease in children.

All but one of the 31 patients with CP had histologic evidence of gastritis. Since the one exception lacked antral biopsy material, antral gastritis could not be ruled out. Overall, 55% of patients who underwent antral biopsy



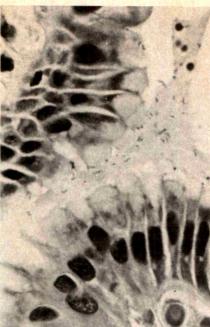


Fig 2.—Left, Biopsy specimen of gastric antrum shows chronic gastritis with diffuse infiltration of lamina propria by lymphocytes and plasma cells (cell type cannot be resolved at this magnification). Occasional foci of glandular inflammation (arrows) show acute (neutrophilic) infiltration (hematoxylin-eosin, original magnification × 140). Right, Highmagnification view of surface epithelial cells and gastric mucous coat shows bacilli with loose spiral configuration characteristic of *Campylobacter pylori* (hematoxylin-eosin, original magnification × 1400).

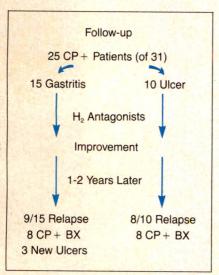


Fig 3.—Follow-up data were available on 25 of 31 patients in whom *Campylobacter pylori* (CP) was identified on biopsy (BX) of gastric antrum or fundus. All patients responded to acid (H₂)—antagonist therapy. However, within one to two years, nine of 15 patients with gastritis had symptomatic relapse with CP again identified on second gastric BX. Three patients developed peptic ulcer during follow-up. Eight of ten patients with peptic ulcer at outset had relapses during follow-up and CP was identified on second BX.

with histologic gastritis had CP present, and there was a clear relationship between the presence of CP and increased severity of gastritis. It also appears that patients with CP gastritis tend to have a different quality of gastritis, with the majority having predominantly chronic inflammation with focal acute glandular destruction, while more patients without CP had purely chronic inflammation.

The predominance of chronic inflammation in children with CP differs significantly from the descriptions of CP gastritis in adults, in whom a more diffuse acute inflammatory component is present in the lamina propria as well as in many glands. Acute inflammation in the children in the present series was limited to relatively few glandular foci. The importance of this observation is uncertain. Perhaps the chronic inflammation observed in the younger subjects in the present study represents an earlier phase of infection. Early CP infection in the experimental gnotobiotic piglet is characterized by a chronic inflammatory response.11

Eight (89%) of nine patients in the

present study who had duodenal ulcer had CP identified in the gastric antrum. The increased prevalence of endoscopically diagnosed duodenal ulcers in the patients with CP suggests an association between presence of the organism and acid-peptic disease in children. However, an inverse association with respect to those patients with gastric ulcers is puzzling: only one (11%) of nine children with gastric ulcers was found to have CP on biopsy. Studies in adult populations have frequently shown a strong association of CP with both duodenal and gastric ulceration. Marshall and Warren² found gastric CP to be present in 77% of patients with gastric ulcer and in 100% of those with duodenal ulcer; similarly, Buck et al⁵ noted gastric CP in 59% of patients with gastric ulceration. In another study, Price et al4 reported CP in cultures from 81% of patients with duodenal ulcers and 57% of patients with gastric ulcer. In a pediatric population, Drumm et al8 showed CP to be present in two patients with duodenal ulcers and two of four patients with gastric ulcers. The significance of the inverse relationship found in the present study is not clear: it may indicate that the epidemiology of gastric ulceration with respect to the role of CP is different for pediatric populations.

It should be noted that several patients with antral CP had endoscopically normal mucosa; thus it would be unwise to assume that a normal appearance on endoscopy precludes the need for biopsy.

While the present study adds to the accumulating evidence of an association between gastritis, duodenal ulceration, and CP, the organism's role as a primary pathogen or an opportunist remains to be determined. Follow-up data on the 25 patients treated with H₂-antagonists show initial symptomatic improvement in all patients and endoscopic resolution of ulcers in ten of 11 patients with ulcer. However, there was a high rate of relapse one to two years later, and CP was present in these patients on repeated biopsy. Price et al4 reported similar findings in three patients with duodenal ulcers, who showed persistence of CP after treatment with H2 antagonists despite

healing of ulcers. These findings may indicate either the reemergence of CP after partial eradication by weak antimicrobial action of H₂ blockers or recolonization after recurrence of the primary pathologic lesion, with CP being merely an opportunistic infection.

It is of note that 30 of 31 CP-positive patients had organisms readily identifiable on routine HE-stained slides, with CP detected in only one addi-

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tional patient by Giemsa staining. In addition, we have for the past three years been culturing all gastric endoscopic biopsy material for CP, and have had 89% correlation between culture results and histologic identification of organisms with HE staining (S.J.C., unpublished data, 1987). Other investigators have reported similar findings.¹²

Future work with such patients, including trials of antimicrobial therapy,

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may help to elucidate further the role of CP infection in pediatric gastritis and peptic ulcer disease. If such studies continue to mirror experience with adult populations in which antibiotic therapy is associated with eradication of organisms and symptomatic and histologic resolution of lesions,¹³ it seems likely that we will be developing new approaches to the diagnosis and management of these diseases in children as well.

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In Other AMA Journals

ARCHIVES OF DERMATOLOGY

Scalp Colonization by *Trichophyton tonsurans* in an Urban Pediatric Clinic: Asymptomatic Carrier State

Vidya Sharma, MD; John C. Hall, MD; Jane F. Knapp, MD; Sumadeep Sarai, MD; Dorthiel Galloway, RN; Dennis E. Babel, PhD (Arch Dermatol 1988;124:1511-1513)

Screening for Psychosocial Disorders in Pediatric Practice

Michael S. Jellinek, MD, J. Michael Murphy, EdD

 Pediatricians have traditionally placed a high value on screening procedures. Screening tests are a routine part of health maintenance visits and serve the dual function of prevention and early recognition. However, despite the high prevalence of psychiatric disorders, there is no psychosocial screening procedure available. We present the Pediatric Symptom Checklist (PSC), a one-page, 35-item, parent-completed questionnaire that screens school-age children for psychosocial dysfunction. The PSC is administered in the waiting room and can be completed and scored in under five minutes. The PSC is not diagnostic of specific psychiatric disorders but is designed to help the pediatrician select which children may benefit from further clinical evaluation.

(AJDC 1988;142:1153-1157)

Although epidemiological studies indicate that 5% to 15% of schoolage children have psychiatric disorders1,2 and that many others face the stresses of divorce, chronic disease, and poverty, studies of outpatient pediatric practice demonstrate that only a small percentage of children with such disorders are identified by their pediatricians. 3,4 There are many reasons for pediatricians' difficulty identifying psychosocial problems: (1) Pediatric residents receive limited training in primary care and even less that is specifically directed at the recognition and evaluation of psychosocial problems. 5 (2) Insurance carriers provide minimal coverage for the primary care pediatrician's evaluation or treatment of psychiatric disorders, and managed care plans rarely encourage utilization of child mental health services: (3) Psychosocial disorders are often not evident in brief office visits and frequently come to attention only by parent complaint late in their course.

One approach that could lead to earlier and more accurate pediatric recognition of psychosocial disorders would be use of an effective screening procedure in the pediatrician's office. To fit into the pattern of clinical practice, a psychiatric screening procedure would have to be similar to other office-based screening measures (hematocrit determination, growth charts) in being brief, valid, inexpensive, easy to use, and clinically relevant. The screening process would have to be specific in selecting the appropriate children for further evaluation and sufficiently sensitive not to miss children who might benefit from further assessment.6

PSYCHIATRIC SCREENING INSTRUMENTS AND MEDICAL PRACTICE

Systematic screening for psychiatric disorders in adults started during World War II as part of the induction process for new recruits. After the war, the Cornell Medical Index, the General Health Questionnaire, and the Hopkins Symptom Checklist were developed to be used in primary health care settings. These questionnaires achieved sensitivities and specificities of 0.70 to 0.80 in studies screening adult patients for anxiety and depression. Murphy,7 in an excellent review of adult mental health screening instruments, recommends that future questionnaires emphasize brevity, a focus on impairment in daily functioning, relevance to the primary care physician, and carefully considered criteria for validation.

We reviewed the literature^{8,9} for parent-completed questionnaires that identify children with psychiatric disorders¹⁰ and found that the four most commonly used questionnaires, Achenbach's Child Behavior Checklist (CBCL),^{11,12} Conners' Parent Rating Scales,^{13,14} Miller's Louisville Behavior Checklist,¹⁵ and Lessing's Institute for Juvenile Research Checklist,¹⁶ were designed for use in mental health settings or for psychological research.

These four instruments are lengthy, containing 70 to 274 questions, and generate tentative diagnostic subscales with little clinical relevance for the pediatrician. The CBCL, the most thoroughly validated screening questionnaire, is ill-suited for screening in a busy pediatric office practice because of the time it takes to administer and score. Two shorter questionnaires, the Quay-Peterson17 and the revised Conners,14 do not appear to have been validated for use as screening questionnaires. A third, Rutter's Behaviour Questionnaire, 18 is brief (31 items) and has been validated in England as a first-stage screen in a large, carefully designed epidemiological study; however, the questionnaire has a low specificity rate, resulting in large numbers of children being considered in need of further evaluation. Because our review of the literature found no screening questionnaire specifically designed for use in pediatric office practice, we developed the Pediatric Symptom Checklist (PSC) for this purpose (Table). 19

CONCEPTUAL AND RESEARCH ISSUES

There are a number of conceptual issues relevant to psychosocial screening in pediatric practice: (1) Should screening be based on an interview or a questionnaire? (2) When screening for psychosocial disorders in schoolage children, should the child, the parent, or both be screened? (8) How should the screening procedure be focused, scored, and interpreted? (4) How can a psychosocial screening procedure be validated?

Given the rapid pace of pediatric practice, a screening procedure must be brief. Other pediatric screening methods, such as hematocrit determination and urine testing, can be performed and interpreted within several minutes during a routine office visit. Ideally, psychosocial screening should also be completed within a few minutes, at a minimum cost of professional time, and should fit easily within the

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culture of pediatric practice. A questionnaire that could be completed quickly, require little time from the clinician, and be easy to score and interpret should fit well into pediatric office practice. Such a questionnaire could easily be given once or twice annually.

Who should complete the questionnaire? Recent research indicates that parents and children agree to only a moderate degree in their reports of children's symptoms.20 Children report higher rates of intrapsychic distress, such as dysphoria, anxiety, and phobia; parents report more behavior problems and generally provide a more comprehensive and historically accurate source of information.21 Considering the broad focus of a pediatric screening questionnaire, and the limited time available, a parent-completed questionnaire appears to be the most reasonable approach for routine screening of school-age children.

How should a parent-completed questionnaire be focused? Should questions screen for the epidemiologically most prevalent psychiatric disorders, or should the questionnaire assess the child's daily functioning (family, school, friends, play, and mood)? Pediatricians are taught to focus on development and functioning and thus are not as familiar with specific (and changing) criteria for psychiatric diagnoses. Neither psychosocial dysfunction nor psychiatric diagnoses are completely objective and both at some point in the diagnostic process require subjective judgment.

How much dysfunction in what developmental areas justifies a positive screening? Is the presence of any psychiatric diagnosis, without regard to severity or kind, sufficient to justify a positive screen? Recent studies22 using standardized psychiatric interviews have found that using current diagnostic standards, a number of diagnoses are relatively common in children. Some conditions, such as attention deficit disorder and oppositional disorder, can range from negligible to severe in their impact on daily functioning. Thus, the mere presence of a diagnosis does not provide much help to the pediatrician who wishes to make a screening decision. Similarly, the absence of a psychiatric diagnosis

| Pediatric Symptom Checklist | | | | | | | | |
|-----------------------------|---|--|--|-------|--|--|--|--|
| Ple | ase mark under the heading that best fits your child: | | | | | | | |
| | | Never | Sometimes | Often | | | | |
| 1. | Complains of aches or pains | | | | | | | |
| 2. | Spends more time alone | | | | | | | |
| 3. | Tires easily, little energy | *************************************** | | | | | | |
| 4. | Fidgety, unable to sit still | | *************************************** | | | | | |
| 5. | Has trouble with a teacher | | | | | | | |
| 6. | Less interested in school | | *************************************** | | | | | |
| 7. | Acts as if driven by a motor | - | | | | | | |
| 8. | Daydreams too much | ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ | *************************************** | | | | | |
| 9. | Distracted easily | | w_named report | | | | | |
| 10. | Is afraid of new situations | Angelous de la companyone de la companyo | | | | | | |
| 11. | Feels sad, unhappy | | *************************************** | | | | | |
| 12. | Is irritable, angry | | areas and a second a second and | | | | | |
| 13. | Feels hopeless | | | | | | | |
| 14. | Has trouble concentrating | - | | | | | | |
| 15. | Less interest in friends | | *************************************** | | | | | |
| 16. | Fights with other children | | - Carrier Company | | | | | |
| | Absent from school | | *************************************** | | | | | |
| 18. | School grades dropping | | ATTENDED TO THE PARTY OF THE PA | | | | | |
| | Is down on him or herself | | ALCOHOLD COMP. | | | | | |
| 20. | Visits doctor with doctor finding nothing wrong | | ***** | | | | | |
| | Has trouble with sleeping | *************************************** | | | | | | |
| 22. | Worries a lot | | www.com/chicks | | | | | |
| 23. | Wants to be with you more than before | *************************************** | | | | | | |
| 24. | Feels he or she is bad | | *************************************** | ., | | | | |
| 25. | Takes unnecessary risks | | *************************************** | | | | | |
| 26. | Gets hurt frequently | | | | | | | |
| 27. | Seems to be having less fun | *************************************** | | | | | | |
| 28. | Acts younger than children his or her age | | | | | | | |
| | Does not listen to rules | ********* | *********** | | | | | |
| 30. | Does not show feelings | | | | | | | |
| | Does not understand other people's feelings | ,, | ************************************** | | | | | |
| 32. | Teases others | | | | | | | |
| 33. | Blames others for his or her troubles | | ************* | | | | | |
| 34. | Takes things that do not belong to him or her | | | - | | | | |
| 35. | Refuses to share | | *************************************** | | | | | |

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should not automatically imply a negative screen. Some common problems, such as an adjustment to a school failure or hostile parental divorce, do not fit neatly into psychiatric diagnostic categories, yet in pediatric practice are typical issues that may deserve attention. Although psychiatric symptoms should not be ignored, we believe that the weight of evidence favors a screening procedure focusing on the "bottom line" of daily functioning rather than the presence of specific psychiatric diagnosis.

How should a parent-completed screening questionnaire that assesses psychosocial functioning be scored? Should there be several clusters of questions addressing specific areas of functioning, eg, school or family relationships, and then each area scored separately, with dysfunction in any single cluster justifying further evaluation? Alternatively, should all areas be grouped together so that the questionnaire can generate a single score cutting point that determines the need for further assessment? If the criteria were to be dysfunction in any one of

the areas of a child's life, then the percentage of children screened positive would probably be overwhelming to the busy pediatrician. Furthermore, school-age children who are doing well overall, but who have difficulty with a teacher, fail a subject, or are facing a transient family stress, often recover without intervention. Children with serious dysfunction are more likely to manifest difficulty in multiple areas. For example, a child overwhelmed by a discordant divorce will often have academic problems or difficulties with one or both parents, will be less available to friends, and will have a dysphoric mood.23 Given the time constraints of pediatric practice, use of a single global cutting score would limit positive screening to the group of children dysfunctional in multiple areas of daily life and would probably identify enough at-risk children to keep most pediatricians busy. From a practical perspective, such a single clinically relevant score is highly desirable and parallels laboratory tests already familiar to pediatricians.

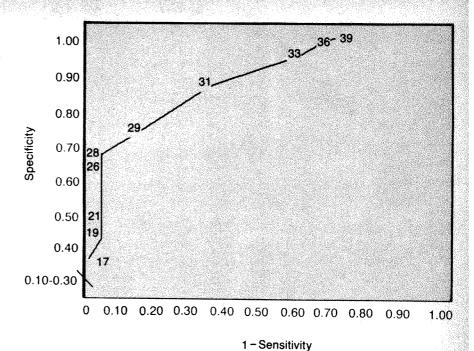
Based on these judgments concerning method, time frame, focus on daily functioning, and use of a single cutting score, we developed the PSC (Table), a 35-item questionnaire that can be completed by parents of 6- to 12-year-old children in the waiting room during a routine pediatric office visit. The PSC is designed to be completed and scored in under five minutes and to yield a single score that, if above a specified cutting point, indicates the need for further assessment of psychosocial problems by the pediatrician.

The PSC began as a shortened and substantially revised form of the Washington Symptom Checklist.24 It was piloted on a general pediatric ward, where it appeared useful in identifying children who might benefit from further psychiatric consultation.25 The questionnaire was then revised based on clinical impressions about indicators of children's overall functioning, an examination of items from other questionnaires, and the diagnostic criteria for children listed in the American Psychiatric Association's DSM-III.26 Given the brevity of the instrument as well as a desire to review, for the pediatrician, all major areas of the child's functioning, we did not attempt to use the item analysis data to shorten the PSC any further. The final version is a single page list of 35 questions that are answered "Never," "Sometimes," or "Often." A score is obtained by assigning 0, 1, and 2 points, respectively, to each answer and adding the total number of points. The PSC score is not "truth," but reflects a parental impression of the child's psychosocial functioning. The critical question that then remains is whether the PSC is valid: Are the children screened positive truly dysfunctional and in need of further evaluation? Are the children screened negative truly "well"?

VALIDATION STUDIES

Because there are no objective or biochemical tests that directly measure psychosocial dysfunction, the validation of the PSC followed the currently accepted method of relying on multiple measures, a variety of approaches, and rigorous research methods.^{27,28}

The first validation study of the



Effect of Pediatric Symptom Checklist cutoff scores on screening results.

revised PSC compared it with the longer, well-validated CBCL. Parents of 206 school-age children completed both the PSC and the Behavior Problems section of the CBCL during routine office visits. After a pilot sample was used to establish a likely PSC cutting score (28 points or above was defined as a positive screening), the results of screening with the PSC and CBCL were compared. The two questionnaires agreed for 89% of the children screened, and both yielded positive screening rates of approximately 15%; κ was .52.10,19 In a second study, the PSC was administered to the parents of school-age children being referred to a clinic for psychiatric or psychological evaluation. Ninety percent of the 31 children in the sample were screened positive on the PSC, including all of the children clinically assessed to be functioning poorly or very poorly.19

A third study was designed to evaluate the rate of agreement between the PSC and comprehensive assessments of the functioning of 6- to 12-year-old children seen routinely as pediatric outpatients. Forty-eight children (28 screened positively by the PSC and 20 screened negatively) were randomly selected from two outpatient pediatric practices. The children's PSC scores were compared with (1) blind ratings of overall func-

tioning by an experienced psychologist and psychiatrist using the Children's Global Assessment Scale (CGAS)^{29,30}; (2) results from a structured psychiatric interview, the Diagnostic Interview for Children and Adolescents, Parent Version (DICA-P)³¹; (3) total recent life stress score as measured by the Life Events Scale for Children (LES)³²; (4) ratings of the children's functioning by their pediatricians; and (5) current and/or past psychiatric treatment.

Findings indicated that when compared with psychologist/psychiatrist CGAS ratings, the PSC with a cutoff score of 28 has a sensitivity of 0.95 (an acceptably low rate of false-negative results) and a specificity of 0.68 (a false-positive rate of approximately 1/3); k was .60.33 The Figure presents a Receiver Operator Characteristics (ROC) curve³⁴ that illustrates the effect of changing the PSC screening score when using the CGAS as the validity standard. The ROC analysis allows assessment of screening test performance by providing information about the trade-offs involved in raising and lowering cutoff points on the test. As the Figure shows, the currently defined cutting score of 28 (along with scores of 26 and 27 in this sample) is the closest to the ideal. Using a higher cutting score of 33 lowers the falsepositive rate to only 7% but increases

the percentage of false-negative results to 55%. At the opposite extreme, a cutting score of 17 misses none of the "true cases" (children with clinician-rated serious dysfunction) but leads to more than half the children being screened positive and a false-positive rate of 39%. As the ROC curve suggests, a cutoff score of 28 provides an optimal balance for pediatric practice and the strongest overall association between PSC cutting score and the ratings of experienced clinicians.

Although the false-positive rate of 0.32 is not optimal, it is acceptable since the recommended intervention is a ten- to 15-minute pediatric review to assess clinically the child's psychosocial functioning. When presence of a serious *DSM-III* diagnosis (excluding enuresis and phobia) on the DICA-P was used as the validity standard, the sensitivity of the PSC was 0.87, the specificity was 0.89, and the κ was .74.

Although the relationship between life stresses and psychosocial dysfunction is often indirect or nonexistent, we would expect to find some relationship between stress and daily functioning. In this study, the mean stress score of the children screened positive by the PSC was almost twice as high as for the children screened negatively by the PSC (mean score = 96.1 vs 49.0; P < .001).

A slightly different kind of relationship was hypothesized between the PSC as well as both pediatricians' ratings and ratings of whether the children were receiving therapy. Although some level of agreement would be desired, a useful screening instrument would have to identify previously undetected cases. Virtually all (ten of 11) of the children currently receiving some form of psychological treatment had positive PSC screening scores; the need for screening was demonstrated by the finding that more than half of the children with positive PSC scores were not currently receiving any form of therapy. The PSC performed similarly when compared with pediatricians' ratings of overall functioning; the checklist flagged ten of 11 children rated by their pediatricians as needing further evaluation, but approximately half of the children screened positively by the PSC were not recognized by their pediatricians.

The test-retest reliability of the

PSC in this study was acceptable (overall Pearson correlation, r=.86 between two administrations of the PSC about four weeks apart). Case/noncase identifications at the two times agreed in 77% of the cases. Intratest reliability, as calculated by Cronbach's α , was r=.89. 35

In a fourth study, PSCs were completed by the parents of 300 consecutive pediatric outpatients. Forty-two of these children were from lower middle class backgrounds and 70 were from minority groups. Although being a member of a minority group had virtually no effect on PSC screening scores, being economically disadvantaged did (24% screened positive vs 13% for the rest of the sample).33 These children, in addition to the stress of economic disadvantage, were more likely to have experienced family discord, including divorce, to currently be living with a single parent, and to have experienced greater numbers of life stresses.

These findings have been replicated independently by other investigators in a very different population, where the PSC was used to screen 260 6- to 12-year-old children as part of a program that provided physical examinations for elementary schoolchildren on a military base (W. O. Walker, MD, R. G. Lagrone, PhD, A. W. Atkinson, MD, unpublished data, September 1986). A random sample of 42 of these children were seen for in-depth interviews by a pediatrician and an experienced child psychologist. Using the clinicians' consensus CGAS ratings (blind to PSC scores) as the validity standard, the PSC achieved a sensitivity of 0.87, a specificity of 0.70, and an overall agreement between the clinicians and the PSC of 75%.

In our most recent study, the PSC was used in a school setting to assess whether a positive screening score was associated with aspects of academic functioning. The PSCs were completed during the first half of the school year by the parents of 140 of the 166 students in a cluster of classes in a public junior high school (J.M.M., M.S.J., S. Milinsky, unpublished data, 1988). Ratings on the parent PSC agreed with counselor assessments of student dysfunction (blind to PSC scores) for 83% of the students ($\kappa = .35$). Of the 24 students screened

positively by the parent PSC, ten (42%) went on to fail at least one course, compared with only 11 (10%) of the 114 students screened negatively by the parent PSC (P=.001). Although the most important criterion for the validity of the PSC is a clinician's determination of the child's psychosocial functioning, these schoolbased variables provide objective, real-world indicators of how children are doing in one of the most important areas of daily life. The results of this study document the validity of the PSC against standards that are independent of parental reports.

COMMENT

Pediatric practice is changing, with a greater need to be aware of children's psychosocial needs (J.M.M., M.S.J., S. Milinsky, unpublished data, 1988). Whether based on increasing recognition, new knowledge, or a rising true prevalence, between 5% and 15% of children have substantial psychosocial difficulties that are clinically relevant to pediatricians. Unfortunately, despite the advocacy of leading pediatricians and professional organizations,36 changes in practicing pediatricians' recognition of psychosocial disorders have come very slowly, and referral rates (1% to 2%) continue to be far lower than the estimated need.4 The PSC has been developed specifically to address the problem of initial recognition by pediatricians of psychosocial dysfunction in school-age patients. The questionnaire designed to fit the culture of outpatient pediatric practice and has been well accepted by parents. It is brief, practical, easy to score, and yields a single cutting score that has been shown to have high rates of agreement with a number of other indicators of psychosocial and psychiatric functioning.

Using the data from our studies, we can now estimate that in a busy pediatric practice that encounters about 50 6- to 12-year-old children a week, approximately 48 parents would complete the PSC and seven (14%) of the children would be screened positive. Three of the seven children would already be known to their pediatricians and probably receiving treatment, one child would be a false-positive finding with only mild difficulties

or overly anxious parents, and three children would be newly recognized as having serious psychosocial dysfunction. The PSC does not attempt to oversimplify psychosocial disorders because its goal is to screen rather than to diagnose. The specific clinical needs of the patients and families are not determined by the screening test but rather on subsequent pediatric evaluation or, if indicated, referral to a mental health clinician. It is hoped that the PSC will encourage communication between parents and pediatricians, tacitly by being placed and collected in the pediatric waiting room and explicitly as the pediatrician discusses with parents the results of the

Our research suggests that the use of the PSC will not add much time to a busy pediatrician's schedule. For many children, a negative PSC screening score may save several minutes

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that are now spent on a spotty, subjective review. For others screened positive but well-known and already receiving needed services, no further time is required. However, for about 5% of the school-age children seen, a positive PSC screen can alert the pediatrician to a child's clinically relevant and previously undetected dysfunction.

The final component of screening, integration into clinical practice, raises multiple questions that depend more on value judgments than on the technical qualities of the instrument. Assuming that an ideal psychosocial screening measure was available, would pediatricians implement the process from screening through to referral? A parallel issue exists in adult medicine, where high-quality screening instruments are currently available for the diagnosis of depression. Although epidemiological studies in-

dicate a substantial prevalence of this disorder in primary care settings and that the efficacy of psychiatric treatment of depression is above 70%, few internists screen for this common, treatable disorder.³⁷

Will pediatric residents be trained to evaluate psychosocial dysfunction? Will parents be responsive to this broader scope of pediatric assessment? Do pediatricians have confidence in the available mental health resources? Will third parties reimburse for these pediatric and mental health services? Although the answers to these questions will be determined by parents, pediatric leaders, or third-party administrators, the implementation of a screening procedure will ultimately be based on society's judgment as to the value of children's psychosocial development and its readiness to allocate resources to remediate dysfunction.

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1157

Polymicrobial Bacteremia in Children

An 11-Year Experience

William A. Bonadio, MD

 The clinical records of all patients with blood cultures positive for a bacterial pathogen were retrospectively examined during an 11-year period to determine the rate of and clinical features associated with polymicrobial bacteremia. During this period, bacteria were isolated in 6302 blood cultures. Of these cultures, 38 instances (0.6%) of polymicrobial bacteremia occurred in 38 patients. In 37 patients (97%), an underlying condition was identified that was considered a predisposing factor for polymicrobial bacteremia-18 patients (42%) had lesions of the gastrointestinal tract, 13 patients (34%) had an indwelling central venous catheter, nine patients (24%) had a malignant neoplasm or were receiving chemotherapy, and nine patients (24%) had neutropenia. A total of 98 pathogenic organisms were isolated; 52 were gram-negative and 46 were gram-positive, and 18 patients (47%) had more than two organisms isolated. Polymicrobial bacteremia was usually clinically indistinguishable from monomicrobial septicemia. Overall mortality was 32%. Polymicrobial bacteremia continues to be a rare, but serious, Infectious disease that usually affects children with underlying medical problems and is associated with a high rate of mortality.

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Bacteremia is common in children. When multiple organisms are isolated from a single blood culture, it usually denotes the presence of contaminant bacteria with or without a true pathogen. It is uncommon for two or more pathogenic organisms to in-

vade the bloodstream either simultaneously or during the same illness; usually this occurs in a host with an underlying immune deficiency or anatomic abnormality and is associated with a high mortality rate. Examples include patients with malignant neoplasms undergoing chemotherapy or children with significant burns.

Few reports describe polymicrobial bacteremia in children. The purpose of this study is to identify children with polymicrobial bacteremia during an 11-year period in an effort to define their clinical features, course, and outcome.

METHODS

The results of all blood cultures performed on patients at Children's Hospital of Wisconsin, Milwaukee, from 1977 to 1988 were surveyed. All cultures in which more than one organism was isolated were recorded, and the medical records of these patients were reviewed. In this study, Staphylococcus epidermidis, Propionibacterium, diphtheroids, and other common skin contaminants were not considered pathogens and were excluded unless the patient had a clinical course consistent with septicemia and at least two successive cultures within a 72-hour period that yielded these organisms. Neutropenia was defined as an absolute neutrophil count less than 1.0×10^{9} /L when the positive blood culture was obtained.

Blood for cultures was obtained after preparation of the skin with iodine solutions followed by 70% ethyl alcohol. The blood was inoculated into standard pediatric vacuum carbon dioxide blood culture bottles that contained trypticase soy broth and thiol broth. All cultures were incubated aerobically and anaerobically at 35°C, with the aerobic bottle vented in the laboratory. The cultures were examined daily for seven days. Cultures were routinely subcultured at 24 hours and five days; the aerobic plates were incubated for 24 hours in an atmos-

phere of 10% carbon dioxide, and the anaerobic plates were incubated for 48 hours. All organisms isolated were confirmed by traditional microbiologic methods.

RESULTS

During the study period, bacteria were isolated in 6302 blood cultures. In 166 cultures (2.6%), more than one organism was isolated; in 38 instances (0.6%), the criteria for polymicrobial bacteremia were fulfilled, and the patient had a clinical course consistent with septicemia (five other instances were eliminated because of insufficient data). Patient ages ranged from 2 days to 14 years; three patients were younger than 1 month, 14 were ages 1 to 12 months, 13 were ages 1 to 5 years, and eight patients were older than 5 years. A temperature higher than 38°C was present in 31 (77%) of 38 patients when the blood culture was obtained. The presenting features of septicemia caused by polymicrobial organisms usually were indistinguishable from those of a monomicrobial cause. All patients were hospitalized when their episode of polymicrobial bacteremia occurred; with the exception of two patients who died of sudden infant death syndrome, all received parenteral antibiotic therapy.

The profile of organisms responsible for polymicrobial bacteremia and their frequency of isolation are given in Table 1. A total of 98 pathogenic organisms were isolated in the 38 cases; 52 were gram-negative organisms and 46 were gram-positive organisms. In eight instances, an organism usually considered a contaminant was isolated (with at least one other pathogenic organism) in at least two successive cultures performed during a 72-hour period (all were coagulase-negative

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Staphylococcus. In all cases in which a surviving patient had Staphylococcus aureus isolated only once with at least one other pathogenic organism, treatment with vancomycin hydrochloride or an appropriate semisynthetic penicillin antibiotic was administered with subsequent clinical recovery. The only patient who died of sudden infant death syndrome had a single isolate of S aureus in combination with Escherichia coli (heart culture at autopsy). A total of 20 patients had two organisms isolated: 18 other patients (47%) had more than two organisms isolated (14 patients with three organisms and four patients with four organisms). Of 39 organisms isolated in blood cultures of patients with altered skin surfaces, 22 were gram-positive organisms; of 22 organisms isolated in blood cultures of patients with malignant neoplasms, 16 were gram-negative organisms. Of 18 patients with more than two organisms isolated, seven had an indwelling central venous catheter. Of three patients with upper respiratory tract infection, two with tonsillitis had three or more organisms isolated.

The profile of associated underlying or predisposing conditions is given in Table 2; a total of 74 clinical factors were present in 37 (97%) of the 38 patients studied. With regard to outcome, 12 patients (32%) died; five of these patients had an absolute neutrophil count less than $1.0 \times 10^{\circ}/L$ when their episode of polymicrobial bacteremia occurred.

COMMENT

Polymicrobial bacteremia is uncommon. Previous reports1-5 have documented the rate of polymicrobial bacteremia in their respective populations to be from 1.2% to 13%; most of these studies were of adult patients, and some included patients with sequential bacteremia. As opposed to these studies, we documented a lower overall rate of true polymicrobial bacteremia of 0.6%; this is approximately half the frequency observed in the only other study involving children. 1 Many of our patients had an underlying anatomic abnormality; as noted previously,3,6 the most common were of the gastrointestinal tract or associated with the presence of an indwelling central venous

| Table 1.—Bacteriologic F Polymicrobial Bactere | |
|---|--|
| Bacteria | No. of Patients |
| Gram-positive isolates | |
| Streptococcus species | - 14 Tr. 1 - 15 C. |
| Pneumoniae | 4 |
| Group A | 2 |
| Group B | 2 |
| Group D | 1 |
| Other | 7 |
| Staphylococcus species | |
| Coagulase-positive | 12 |
| Coagulase-negative | 8 |
| Enterococcus | 10 |
| Gram-negative isolates | |
| Klebsiella species | 14 |
| Enterobacter species | 11 |
| Escherichia coli | 10 |
| Pseudomonas aeruginosa | 6 |
| Citrobacter species | 4 |
| Proteus mirabilis | 2 |
| Haemophilus influenzae | |
| type B | 1 |
| Salmonella species | 1 |

catheter. Additionally, patients with an underlying immune deficiency were commonly identified, including those with malignant neoplasms undergoing chemotherapy and those with neutropenia. These findings contrast with a previous study¹ of children with polymicrobial bacteremia that found the most common predisposing conditions to be neonatal age (40%), presence of an indwelling catheter (40%), and failure to thrive (23%); an underlying lesion of the gastrointestinal tract was identified in only one of 17 patients, and neutropenia did not occur.

Other

We found an almost equal representation of gram-negative and gram-positive organisms. No combination of pathogens predominated, but children with altered skin surfaces (including those with an indwelling central venous catheter) tended to have grampositive organisms isolated, whereas children with malignant neoplasms undergoing chemotherapy tended to have gram-negative organisms isolated. We considered all cited cases in which a surviving patient with S aureus isolated in a single culture to represent bacteremia since clinical recovery was noted after treatment with an appropriate antimicrobial medication; we were unable to document whether the single isolate of this organism in the child with sudden infant death syndrome played any role in his illness. We found that 47% (18/38) of

| Table 2. | Underlyin | g Conditions |
|----------|--------------|--------------|
| Associa | ated With Po | olymicrobial |
| | Bacterem | ilá |
| | | |

| Underlying Condition | No. of Patients |
|------------------------------|----------------------------|
| Gastrointestinal tract | |
| Peritonitis | 3 |
| Fistula | 3 |
| Hepatic failure | 3 |
| Short-gut syndrome | 2 |
| Intra-abdominal abscess | 2 |
| Bowel obstruction | 3 2 2 2 |
| Rectal abscess | |
| Rectal prolapse | 1 1 |
| Esophageal varices or | |
| endoscopy | 1 💮 |
| Indwelling central venous | |
| catheter | 13 |
| Malignancy | |
| Acute lymphocytic | |
| leukemia | 7 |
| Lymphoma | |
| Rhabdomyosarcoma | 1 |
| Immune deficiency | |
| Neutropenia | 9 |
| Sickle cell anemia | 4 |
| Respiratory tract | |
| Pneumonia | 3 |
| Tonsillitis | 2 |
| Epiglottitis | 1 . |
| Otitis media | 1 ji |
| Pulmonary embolus | 1 |
| Cutaneous | |
| Burns | 2 |
| Visceral-cutaneous fistula | 2 |
| Varicella or impetigo | 1 |
| Neonate or prematurity | 4 |
| Sudden infant death syndrome | 2 1 4 2 2 2 |
| Genitourinary tract fistula | 2 |
| Congenital heart disease | 2 |
| None identified | 1 |
| | |

cultures had more than two organisms isolated, which is a higher rate than any documented previously (Todd and Fromel, 12%; Hermans and Washington,3 13%; Roselle and Watanakunakorn,5 25%; and Kiani et al,6 32%); of the 18 patients with multiple-organism bacteremia, seven (39%) had an indwelling central venous catheter. In accord with previous reports,7.8 we found that children with upper respiratory tract infection and polymicrobial bacteremia tended to have more than two organisms isolated, possibly due to the augmented potential for multiple organism invasion of the bloodstream via an inflamed oropharyngeal mucosa.

Previous studies¹⁻⁶ have documented mortality rates of between 29% and 54% in patients with polymicrobial bacteremia, depending in part on the characteristics of the population studied. Our observed mortality of 32% is within this range, which is consistent with the rate of 29% previously docu-

mented in children.¹ Apparently, no notable improvement in the survival rate has been observed for polymicrobial bacteremia during the past 20 years,³ despite major advances in diagnosis and therapy.

CONCLUSION

Polymicrobial bacteremia in children is a rare, but serious, infectious disorder associated with a high mortality rate. Children who experience polymicrobial bacteremia are usually compromised hosts due to disruption of anatomic barriers or immune deficiency. In general, equal representation of gram-positive and gram-negative organisms characterize the

bacteriologic profile of this disorder; the common pathogens of pediatric monomicrobial bacteremia are underrepresented in children with polymicrobial bacteremia. One must maintain a high index of suspicion for polymicrobial bacteremia when culture results indicate the simultaneous isolation of more than one organism in a susceptible host and consider initiating broad-spectrum antibiotic therapy early whenever this condition is a reasonable possibility.

Larrie Sarff, MD, critically reviewed this manuscript.

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Book Review

Fasting Girls: The Emergence of Anorexia Nervosa as a Modern Disease, by Joan Jacobs Brumberg, 366 pp, \$25, Harvard University Press, Cambridge, Mass, 1988.

The historical roots of any illness provide an important link to the present context in which it is expressed. This could not be more true than in the case of what some believe to be a modern epidemic: the eating disorders, anorexia nervosa and bulimia nervosa.

Indeed, the incidence of eating disorders has risen dramatically over the past two decades. There may be no other psychiatric disorder that represents such an interesting confluence of variables from the sociocultural, familial, individual, and biologic arenas. Equally fascinating is the role that sociocultural attitudes concerning women's physical appearance seem to have in this phenomenal increase. It cannot be understated that culture has a primary determining role in the presentation of these disorders.

Joan Brumberg, the Director of the Women's Studies Program at Cornell University, offers a well-researched and thoughtful contribution in her book, Fasting Girls, regarding the historical aspects of anorexia nervosa. Brumberg offers a cursory review of the contributions of biological and psychological factors to anorexia nervosa. Her most cogent and innovative presentation stems from her research on how women over the past 600 years have used their bodies to express individual needs while concomitantly yielding to cultural attitudes about thinness equaling happiness. She describes two stages in the development of anorexia nervosa. These include the "recruitment" phase, which is more heavily influenced by culture, and the "career" phase, which pertains to the maintenance of the disease due to psychological and biological factors. She offers case histories of medieval figures such as Saint

Catherine of Sienna whose anorexia nervosa represented less an act of cultural pressure for thinness than a pious attempt of individuality through starvation. Today's patients with anorexia nervosa strive less for spiritual attainment and more for perfectionism and physical aestheticism. Brumberg is careful not to confuse these two types of anorexia nervosa but expounds on the similarities in the use of a woman's body to make a statement, whether religious or perfectionistic.

Eating in the 19th century oftentimes was more than just a biological response but again was culturally determined as an act of gentility and discreet charm. Brumberg's most salient point comes from her argument that in promoting a pervasive message that the relentless pursuit of thinness will provide beauty, success, and self-control, our modern culture has come a long way.

For adolescents in particular, with the extreme pressure to form a unique self-identity yet adapt to cultural norms, the use of a concrete expression of self through thinness and fitness is quite attractive. The popular choice to rely on one's body and the way one eats as a primary mode of self-expression does indeed appear similar to choices our female ancestors made during times of cultural chaos regarding female roles.

It is hoped that Brumberg's arguments will leave the reader with an undeniable charge to challenge thoughtless consumerism and acceptance of this female stereotype of beauty and thinness, not only personally but in the broader social context as well.

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Neonatal Neutropenia

Clinical Manifestations, Cause, and Outcome

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 Neutropenia, defined as an absolute neutrophil count that falls below 2.0 × 10%, is being identified more frequently in the newborn intensive care unit and significantly influences clinical decisions regarding therapy. We prospectively identified 119 episodes of neutropenia in 87 infants (6% of admissions). Less than half of the episodes could be attributed to infections. The majority of noninfectious neutropenia episodes were related to specific perinatal events or were of unknown cause. Infants weighing less than 2500 g were more likely to have neutropenia than term infants (13% vs 3%, respectively) and less likely to have neutropenia related to bacterial infections. Short-term survival (89% vs 95%) and long-term survival (74% vs 77%) were not different in infants with infectious diseases compared with those with noninfectious diseases. Mortality was highly correlated with the need for assisted ventilation (20%) or with an absolute neutrophil count of 0.5 × 10°/L (24%). We conclude that the cause of neutropenia and the clinical condition must be carefully evaluated before instituting aggressive therapy for infection.

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The leukocyte count is believed to be the single most important aid for the early detection and screening of the septicemia. 1-8 Neutropenia may be an important prognostic indicator for bone marrow depletion and mortality in sepsis. 4.5 Reference values for the white blood cell (WBC) count have been established for the first 28 days of life by Manroe and colleagues,6 using 905 heel-prick specimens in which total WBC counts were determined for 434 healthy neonates. Although some preterm infants were included, the infants were primarily at term. The data of Manroe et ale demonstrated a peak in the total or absolute neutrophil count (ANC) at 12 to 14 hours of age of 7.8 to $14.5 \times 10^{9}/L$, followed by a gradual diminution of the ANC until a minimum value of 1.8×10°/L was established at 72 hours. The maximum value did not stabilize until 120 hours (5 days of age) at 5.4×10^{9} /L. This range (1.8 to 5.4×10°/L) then stayed constant for the remainder of the 28 study days, with only 1% of neonates having counts falling outside this range. This range is remarkably similar to those established by other investigators.7-9

There are conflicting data regarding the effect of prematurity on the leukocyte count. Several studies1,6-8,10-18 have reported similar indexes in preterm and term infants, but the gestational ages and weights were not well documented and few infants weighing less than 1000 g at birth (or 30 weeks' gestation) were included. There are even fewer data concerning the outcome of extremely immature infants with neutropenia. Before instituting aggressive, potentially harmful therapy for septicemia, the multiple causes of neutropenia and their outcome need to be considered.

We have investigated 119 consecutive episodes of neutropenia in 87 infants, observed over a period of 20 months, to determine the corresponding clinical and hematologic data and outcome of all infants with neutrope-

nia in the neonatal intensive care unit (NICU).

PATIENTS AND METHODS

This study prospectively identified all infants with neutropenia among admissions to the NICU of Rainbow Babies and Childrens Hospital, Cleveland, during the 20 months from June 1, 1983, through Jan 31, 1985. Neutropenia was defined as an ANC calculated from the complete blood cell (CBC) count, which fell below the ranges determined by Manroe et al.6 An episode of neutropenia was defined as the period from the first low ANC until the ANC was in the normal range (repeated at least once). A CBC count was obtained for all infants on admission to the NICU, at any change in clinical condition, and at least weekly during the hospitalization. We were conducting a trial of granulocyte transfusions for septic, neutropenic neonates, and all abnormal CBCs were reported to the investigators in a timely fashion.

The CBC included a nucleated cell count (Ortho ELT electronic counter, Ortho Diagnostic Systems), platelet count, and a 100-cell differential count (Wright-stained coverslip blood smear). The nucleated cell count represented the total WBC count, corrected for the presence of nucleated red blood cells. An ANC was calculated for each CBC count by multiplying the total WBC by the percentage of polymorphonuclear leukocytes and band forms. Metamyelocytes were not included in the ANC. as they occurred so rarely, and their omission did not affect the ANC. An immatureto-total (I-T) neutrophil ratio was also calculated for each CBC count as the combined percentiles of immature neutrophils (band forms, metamyelocytes, and myelocytes) divided by the total percentage of neutrophils in the peripheral blood. Once neutropenia was identified in an infant, CBC counts were repeated and then examined daily or every other day for ANC, I-T neutrophil ratio, and platelet count.

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Neutropenic episodes were defined as "infectious" if the infant had an associated viral or bacterial infection identified by central culture, pneumatosis intestinalis on abdominal roentgenogram, or pneumonia on chest roentgenogram. Blood and cerebrospinal fluid bacterial cultures and urinary latex agglutination were performed for all infants with neutropenia. Nasopharyngeal and urinary viral cultures and stool rotazyme tests were performed when clinically indicated. All neutropenic episodes that could not be correlated with bacterial or viral infections, necrotizing enterocolitis (NEC), or pneumonia were categorized as noninfectious. Episodes of neutropenia in infants who had abdominal distention and guaiac-positive stools, but normal abdominal roentgenograms and no pathogens isolated from stool specimens, and who were successfully refed within three days, were considered to be of unknown cause. Shortterm mortality was defined as a death occurring during the neutropenic episode and long-term mortality as a death occurring before discharge.

Statistical analysis of clinical and hematologic data was performed using analysis of variance, the Student t test, and the χ^2 test. All results are expressed as the mean \pm SD.

RESULTS

Over 20 months, we prospectively identified 119 episodes of neutropenia in 87 infants, representing 6% of all NICU admissions. The mean gestational age and birth weight were 31.6 ± 4.4 weeks and 1612 ± 852 g, respectively.

Infectious vs Noninfectious Causes

More than 60% (73/119) of the total episodes were considered noninfectious. Isoimmune (one episode), postoperative (three episodes), and postexchange transfusion (three episodes) neutropenia represented only 6% of the noninfectious episodes. Nearly half (n=34) of the episodes were related to the perinatal complications. The remaining 44% (n=32) of the noninfectious episodes were of unknown cause. All of these infants had negative bacterial cultures, and all but three of these infants were treated for less than three days with antibiotics.

Less than half of the episodes were infectious in origin. One fifth of these episodes occurred in infants with positive viral cultures, 10 predominantly cytomegalovirus. Seventeen infants

with NEC represented 35% of these episodes. Bacterial infections (17 episodes) accounted for another 35%. Two infants had bilateral infiltrates consistent with pneumonia on chest roentgenogram, that failed to clear on subsequent films.

A comparison of the infants with infectious and noninfectious neutropenia was made. Infants with infectious neutropenia were of older gestational age $(32.0 \pm 4.8 \text{ weeks})$ than infants with noninfectious neutropenia $(30.3 \pm 3.8 \text{ weeks})$ (P<.05). They also tended to be of larger birth weight $(1.7 \pm 1.0 \text{ kg})$ than infants with noninfectious neutropenia $(1.4\pm0.7 \text{ kg})$ (P = .051), but this did not reach statistical significance. There were no significant differences between the two groups with respect to race, sex, route of delivery, one- and five-minute Apgar scores, duration of hospital stay, the number of infants with platelet counts of less than $100 \times 10^9/L$, the day of onset, or the duration of the neutropenia. The infants with infectious episodes had significantly lower total WBC counts $(3.2 \pm 2.0 \text{ vs})$ $5.6 \pm 3.5 \times 10^{9}$ /L, P<.0001), and ANCs $(0.5 \pm 0.4 \text{ vs } 0.9 \pm 0.4 \times 10^9/\text{L poly-}$ morphonuclear leukocytes, P<.0001), and higher I-T ratios $(0.72 \pm 0.24 \text{ vs})$ $0.43 \pm 0.32 \times 10^{9}$ L, P < .0001), but these values did not constitute a differentiation that was clinically useful in individual cases. Short-term survival (89% vs 95%) and long-term survival (74% vs 77%) were not different in infants with infectious diseases compared with those with noninfectious diseases, respectively.

Neonatal Neutropenia as Related to Cause

Infants with bacterial infection–related neutropenias had higher birth weight $(2.2\pm1.1~{\rm kg})$ and gestational age $(34.0\pm0.5~{\rm weeks})$ than infants with neutropenia associated with either viral infections $(1.5\pm0.8~{\rm kg}; 31.2\pm4.6~{\rm weeks})$ or NEC $(1.2\pm0.6~{\rm kg}; 30.0\pm3.8~{\rm weeks})$ (P<.05). The onset of neutropenia due to bacterial and viral infections (days 1 and 3 of life, respectively) was considerably earlier than that due to NEC (20 days of life) $(P<.05,~\chi^2)$. The WBC count was significantly higher and the I-T ratio was

lower in infants with viral infections, but the magnitude of these differences was not sufficient to differentiate viral and bacterial infections (Table 1). There were no differences in the ANC or platelet counts.

Thirty-four infants had neutropenia at birth. Their birth weights $(1.4\pm0.7~{\rm kg})$ and gestational ages $(30.3\pm3.9~{\rm weeks})$ did not differentiate them from the infants with neutropenias of unknown cause $(1.2\pm0.4~{\rm kg}; 30.0\pm3.3~{\rm weeks})$ or infectious cause. They all had negative cultures but had multiple complications of pregnancy, labor, and delivery, although the Apgar scores were not significantly different from the other groups.

Maternal complications included pregnancy-induced hypertension (29%), most frequently treated with methyldopa (Aldomet); bleeding from placenta previa or placenta abruptio (23%); ruptured amniotic membranes for longer than 24 hours before delivery (29%); and infection (27%). Neonatal complications included respiratory distress (92%) from respiratory distress syndrome in 24 infants and transient tachypnea of the newborn in seven infants; grades 3 to 4 intraventricular hemorrhage (24%); metabolic acidosis (62%), usually related to asphyxia (Apgar score, <6) (62%) and respiratory acidosis related to the lung disease (41%). More than half of the infants (56%) required immediate intubation for resuscitation.

Twenty-five infants had 32 episodes of neutropenia of unknown cause. Six of these episodes occurred in infants with the onset of guaiac-positive stools and abdominal distention. Abdominal roentgenograms did not show either pneumatosis intestinalis or signs of NEC. Stool cultures were negative. These infants were all refed, without complications, after a three-day intestinal rest. One infant was in shock, with hypernatremic dehydration and cardiac arrest, and another was dying consequent to birth asphyxia and multiple malformations (onset of neutropenia on day 8 of life). Apart from these eight episodes, three episodes were accompanied by an increase in apneas and bradycardias, two with tachycardia and two with congestive heart failure. Fifteen episodes oc-

Table 1.—A Comparison of the Hematologic Data of the Infectious and Noninfectious
Causes of Neonatal Neutropenia*

| | | | Data by Cause | | |
|-----------------------------------|------------|--------------|------------------------------|------------------|--------------|
| | Infectious | | | | |
| Hematologic Data | Bacterial | Viral | Necrotizing Enterocolitis | Birth Related | Unknown |
| White blood cell count, ×10°/L | 2.8 ± 1.9 | 4.4 ± 2.5† | 2.6 ± 1.6 | 4.5 ± 1.8 | 7.2±4.4‡ |
| Absolute neutrophil count, ×10°/L | 0.6±0.4 | 0.6±0.3 | 0.5 ± 0.4 | 0.8 ± 0.4 | 1.1±0.04‡ |
| Immature-total neutrophil ratio | 0.77±0.20 | 0.51 ± 0.22† | 0.83±0.19 | 0.50 ± 0.33 | 0.31 ± 0.28‡ |
| Platelet count, No. <100 × 10°/L | 5 | 5 | 9 | 10 | 6 |

^{*}All values are the mean ± SD

Table 2.—Duration of Neutropenia in 119 Consecutive Episodes of Neonatal Neutropenia Duration, d Diagnostic No. of % of Episodes Lasting Category **Episodes** (Mean ± SD) Longer Than 1 wk Infectious 49 10 43.8 ± 38.5* 0 Necrotizing enterocolitis 17 5.9 ± 8.1 70.6 17 Bacterial 2.2 ± 2.1 88.2 Noninfectious 70 Birth related 4.6 ± 9.2 79.4 Unknown 32 22.5 ± 44.8 65.6 119 12.5 + 28.8 68.9

^{*}P<.05, when compared with the other causes within the category.

| Table 3.—Neutropenic Episodes in Term Infants Compared With Low-Birth-Weight Infants* | | | | | | |
|---|------------|--------------|-------|--|--|--|
| | No. (%) by | Birth Weight | | | | |
| Criteria | >2500 g | <2500 g | P | | | |
| Incidence | (3) | (13) | <.001 | | | |
| Infants | 15 (17.2) | 72 (82.8) | <.001 | | | |
| Episodes | 15 (12.6) | 104 (87.4) | <.001 | | | |
| Episodes with infectious causes | 12 (80.0) | 33 (31.7) | <.05 | | | |
| Mortality of infants Short-term | 2 (13.3) | 7 (9.7) | NS | | | |
| Long-term | 2 (13.3) | 16 (22.2) | NS | | | |

^{*}Term infants are defined as those weighing more than 2500 g; low-birth-weight infants, those weighing less than 2500 g. NS indicates not significant.

curred in asymptomatic infants and were discovered on a routine CBC count. Although the duration of the neutropenia in these infants was significantly longer (Table 2) than all the other categories of neutropenia, except viral infections, most (n=27) of these episodes lasted only one to four days.

Finally, three infants had neutropenia lasting three to eight days after multiple exchange transfusions, three infants had postoperative neutropenia, and one had isoimmune neutropenia.

Comparison of Neutropenia by Birth Weight

We found that the low-birth-weight (LBW) infants (those weighing less than 2500 g) admitted to the NICU had a higher incidence of neutropenia

than the infants with birth weights greater than 2500 g (13% vs 3% incidence, respectively; P < .001) (Table 3). Multiple episodes of neutropenia occurred in 20 LBW infants and were more common in the very LBW infants (those weighing less than 1500 g). None of the term infants experienced more than one episode of neutropenia. Although there was no difference between term and LBW infants with neutropenia in either short- or longterm survival, the term infants were more likely to have neutropenia of an infectious cause, compared with the LBW infants (80% vs 32%, respectively; P<.05). Also, more LBW infants had episodes of neutropenia of unknown cause (P<.05), compared with term infants (Fig 1).

Comparison of Neutropenia by Race

The incidence of neutropenia was similar in black infants and white infants (59% vs 41%, respectively). However, black infants were more likely than white infants to have birthrelated neutropenia with negative cultures (51% vs 22%, respectively; P<.01) and less likely to have bacterial infection—related neutropenia (12% vs 31%, respectively; P<.05).

The Onset and Duration of Neutropenia

Neutropenia was most likely to occur in the first week of life (55.5%), with 43% of the total episodes beginning on the first day of life. The incidence of episodes of neutropenia occurring in subsequent weeks of life decreased dramatically after the first week (Fig 2).

The duration of the neutropenia ranged from one to 205 days (Table 2). The median duration was only two days, and 70% of all the episodes lasted less than one week. Among the infectious causes, viral neutropenia lasted significantly longer than neutropenia related to either NEC or bacterial infections (P<.01). Similarly, among the noninfectious causes, the episodes of unknown cause lasted longer than the birth-related episodes (P<.05).

Ninety-four of the episodes of neutropenia consisted of at least two low ANCs. Twenty infants had 25 neutro-

[†]P<.05, compared with the other infectious causes.

[‡]P<.05, compared with birth-related causes.

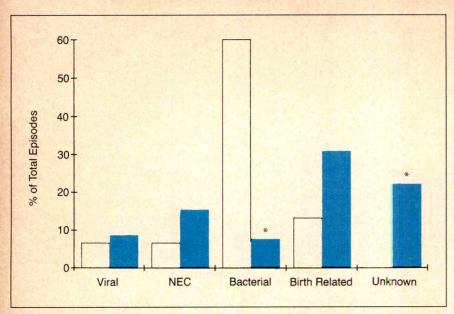


Fig 1.—Comparison of episodes of neutropenia in low-birth-weight and term neonates indicates that low-birth-weight infants are significantly less likely to have neutropenia secondary to bacterial infection and more likely to have neutropenia of unknown cause. Open bar indicates infants with a birth weight of greater than 2500 g; solid bar, infants with a birth weight of less than 2500 g; NEC, necrotizing enterocolitis; and asterisk, P<.05.

| Table 4 | | f the Neutropenic E gree of Neutropenia | A CHARLES AND ADDRESS OF THE PARTY OF THE PA | to the |
|-------------------------|-------------------------|--|--|-----------|
| | No. of | ANO 400/I | Surviv | al, %† |
| ANC Category, ×10°/L | Neutropenic Episodes | ANC, ×10°/L (Mean±SD) | Short-term | Long-term |
| >1.5 | 9 | 1.6±0.1 | 100 | 100 |
| 1.0-1.5 | 29 | 1232 ± 129 | 100 | 93 |
| 0.5-1.0 | 47 | 0.7 ± 0.2 | 98 | 85‡ |
| ≤0.5 | 34 | 0.2±0.2 | 76‡ | 59‡ |

*ANC indicates absolute neutrophil count.

†Several infants had multiple episodes of neutropenia. Therefore, long-term survival of each episode differs slightly from long-term survival of each infant experiencing neutropenia (79%). ‡P<.05.

penic episodes in which there was only a single low ANC. In most cases, there was a delay before the second CBC count was obtained, usually longer than six to eight hours. Twelve episodes occurred, with the first CBC count obtained after birth, and appeared to be related to the complications of pregnancy, labor, and delivery. These infants had an ANC of $0.9 \pm 0.4 \times 10^{9}$ /L and an I-T ratio of 0.48 ± 0.35 . The second WBC count was usually normal or high, with a left shift. Five infants were infected: two with Escherichia coli, one with Klebsiella pneumoniae, one with group B Streptococcus, and one who showed new infiltrates on chest roentgenogram. The ANC of this group was $0.9\pm0.4\times10^{9}/L$, with an I-T ratio of 0.64 ± 0.19 . The second ANC was high or normal, with a left shift by I-T ratio. Finally, there were eight episodes of neutropenia in five infants who had an ANC of $1.4\pm0.02\times10^{9}/L$ and an I-T ratio of 0.30 ± 0.18 . Each of these infants had other episodes of neutropenia separated from this episode by a few weeks of normal ANCs.

Mortality of Infants With Neutropenia

The overall, short-term mortality of the episodes of neutropenia was 10% (9/87). The overall, long-term mortality was 21% (18/87). These nine additional deaths all occurred in LBW infants with complex medical prob-

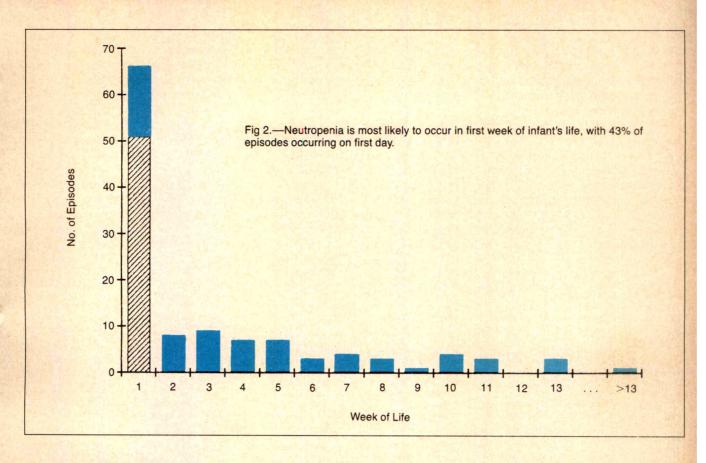
lems. Birth weight, gestational age, race, sex, and cause of neutropenia were all independent of mortality, as determined by contingency table. The need for assisted, mechanical ventilation was highly correlated with mortality (20% [9/44] mortality, P < .005).

The episodes of neutropenia were also categorized according to the degree of neutropenia (Table 4). Of 119 episodes, the lowest ANC in nine episodes was greater than 1.5×10°/L. Short- and long-term survival was 100%. The lowest ANC in 29 episodes was 1.0 to 1.5 × 10 °/L. Short-term survival remained at 100%. Long-term survival dropped to 93% (27/29). Similarly, when the ANC was 0.5 to 1.0×109/L, the short-term survival was still 98% (46/47), but long-term survival was only 85% (40/47). When the ANC fell to 0.5×10°/L or less, both short-term (76% [26/34]) and long-term (59% [20/34]) survival dropped significantly (P < .05).

We were simultaneously conducting a prospective, randomized trial of buffy-coat transfusions in neonates with neutropenia with presumed sepsis.14 Only 31 of these 87 infants with neutropenia were eligible for this trial. Eligibility criteria included two successive ANCs of less than $1.5 \times 10^9/L$ prior to randomization and either the signs and symptoms of fulminant sepsis, accompanied by shock and resulting in mechanical ventilation, or roentgenographic confirmation of NEC, as evidenced by intestinal pneumatosis, with or without biliary tree air on abdominal roentgenogram. All nine short-term deaths occurred in studyeligible infants. There were no infants whose condition worsened after the diagnosis of neutropenia and progressed in severity until they met the study criteria.

COMMENT

The presence of neutropenia in neonates, as defined by Manroe and colleagues, is being used with increasing frequency in clinical decisions. These decisions include an assessment of the probability of sepsis, 1-3 the necessity for performing a bone marrow aspiration to determine prognosis, 4.5 and the need for adjuvant therapy, which might include fresh-frozen plasma,



gamma globulin therapy, and exchange or granulocyte transfusions, in addition to antibiotic and supportive therapy alone. Therefore, it becomes necessary to determine the incidence, time of onset, duration, causes, and prognosis of neutropenia in both afflicted term and preterm infants.

Our 6% overall incidence of neutropenia was much higher than expected. The frequency of neutropenia increased significantly with diminishing birth weight and was greatest in infants weighing less than 1000 g (30%). Several interpretations are possible. The reference ranges established by Manroe et al6 or Xanthou7 were based on data obtained from infants weighing more than 1500 g. The higher incidence of neutropenia of unknown cause in LBW infants compared with term infants in our study may reflect the inapplicability of these values for immature infants. Lloyd and Oto12 examined serial CBC counts in "healthy" infants younger than 33 weeks' gestational age (mean birth weight and gestational age, 30.4 weeks and 1510 g, respectively) and found that from 12 hours to 5 days of age, one

third of the infants had leukocyte counts outside the ranges established by Manroe et ale and Xanthou,7 and initially most of the values were low. Similarly, Coulombel et al11 found lower ANCs in infants younger than 32 weeks of gestational age, compared with those who were 32 to 37 weeks and older than 37 weeks of gestational age. The rate of decrease in the ANC 24 hours after birth was greater in the more mature infants so that the counts were similar by four days of life. However, Coulombel et al studied only six infants younger than 30 weeks of gestational age. There was no long-term follow-up of these infants. The longest study period was that of Manroe et al,6 who followed up the infants' CBC counts for up to one month after birth. Thus, neutropenia in LBW infants may be partly due to physiologic causes.

Alternatively, the normal reference ranges may be applicable to LBW infants who truly have a higher incidence of neutropenia, influenced by either an increased incidence of sepsis or an increased responsiveness to environmental factors. Our data do not

support the supposition that an increased incidence of sepsis is responsible for the increase in neutropenia in LBW infants, who, in fact, were significantly less likely (P < .05) to have an infectious cause identified. Environmental factors undoubtedly do play a role, possibly by release of or depletion of the marginating pool. Certainly, the very LBW infant is more likely to have had complications of pregnancy, labor, and delivery; remained hospitalized longer; experienced more invasive procedures; and been given more antibiotics and other drugs.

The outcome of neonatal neutropenia is equally important as the incidence. Neither the short-term survival nor the long-term survival was different with respect to episodes of infectious compared to noninfectious causes. The decrease in long-term survival reflected the deaths of infants with multiple medical problems rather than sepsis. The need for assisted, mechanical ventilation predicted a 20% mortality, and an ANC falling below 0.5×10^{9} L predicted a 24% mortality. No other factors correlated well

with outcome. It should also be noted that both the short- and long-term survival for neutropenia for our nursery is higher than might be expected from previous reports, 4.5.15 which focus primarily on term infants.

Half of neonatal neutropenia was not proved to be infectious in origin. A few of the noninfectious causes were easily identified and included isoimmune neutropenia and neutropenia following exchange transfusions or surgery. The birth-related episodes occurred in infants with multiple perinatal complications. Neutropenia has

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previously been correlated with some of the following factors: maternal hypertension, periventricular hemorrhage, severe asphyxia, and reticulocytosis. 6.16

In summary, both the incidence of neonatal neutropenia and the survival of affected infants were surprisingly high. More than half of the episodes of neutropenias were noninfectious in origin, but these could not be differentiated from those of infectious cause on the basis of the CBC count. Neutropenia in LBW infants may have a physiologic basis. Low-birth-weight

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Use of Linked DNA Probes for Carrier Detection and Diagnosis of X-linked Juvenile Retinoschisis

Niklas Dahl, MD, Ulf Pettersson, MD, PhD (Arch Ophthalmol 1988;106:1414-1416)

Chronic Osteomyelitislike Disease With Negative Bacterial Cultures

Pirkko Pelkonen, MD; Soini Ryöppy, MD; Jaakko Jääskeläinen, MD; Juhani Rapola, MD; Heikki Repo, MD; Ilkka Kaitila, MD

 During a seven-year period we observed 14 children who had chronic osteomyelitislike disease. The bacterial cultures from the bone lesions were negative. In eight patients the findings were compatible with chronic recurrent multifocal osteomyelitis (CRMO), in four the findings were compatible with chronic sclerosing osteomyelitis of Garré, and two had osteomyelitis of the clavicle. In patients with CRMO, lymphocyte subpopulations, the responses to mitogens, and the chemotactic and chemokinetic responses showed no consistent abnormalities. After a mean followup of 4.5 years (range, one to ten years), all four patients with osteomyelitis of Garré were symptomatic, and two had complications. Only two of the eight patients with CRMO had active disease. The course had been complicated by growth disturbances in one patient and by thoracic outlet syndrome in another. Wegener's granulomatosis later developed in a patient with CRMO.

(AJDC 1988;142:1167-1173)

Bone affections resembling hematogenous osteomyelitis but characterized by a silent and chronic course were first recognized by Garré nearly 100 years ago, when bacteriologic, radiologic, and histologic methods were not available. His name was later linked with chronic lesions situated mainly in the diaphyses of long tubular bones, ie, osteomyelitis of Garré (OMG). Bacteria usually do not grow in these lesions; roentgenograms show marked sclerosis, and micro-

scopic examination shows features of chronic osteomyelitis. 2,3 Osteomyelitis of Garrè is differentiated from chronic osteomyelitis of staphylococcal origin, which has also been called primary chronic osteomyelitis or primary subacute osteomyelitis because of the absence of acute symptoms at onset.4-6 On histologic examination, chronic staphylococcal osteomyelitis often shows an abundance of plasma cells,5 and this was the finding also in three of the four cases of "subacute and chronic 'symmetrical' osteomyelitis" reported in 1972 by Giedion and colleagues.7 However, a bacterial cause was verified in only one of their patients. Their report has been followed by a number of others describing children as well as a few adults with similar clinical and radiologic features and with variable histologic and negative bacteriologic findings.8-17 Today, chronic recurrent multifocal osteomyelitis (CRMO) is an accepted entity17 with well-defined clinical and radiologic characteristics. 9.10 Awareness of these two conditions will save the patient from repeated radiologic investigations and unnecessary chemotherapy.

We observed 14 patients who had chronic osteomyelitis without a proved bacterial cause. We report the findings and outcomes in these 14 patients and the results of immunologic evaluation of the eight patients with CRMO in this group of 14.

PATIENTS AND METHODS

We studied 14 patients at the Children's Hospital, University of Helsinki, from 1977 through 1983. The ages of the patients at onset of symptoms ranged from 3 to 13 years (Table 1). Ten were girls. All patients had osteolytic bone lesions on roentgenograms. Bacterial cultures of biopsy speci-

mens obtained from 13 of the 14 patients were negative for both aerobic and anaerobic bacteria. One patient had a silent course and the lesions healed without antibiotic treatment. Mycobacterial cultures of nine biopsy specimens and mycologic cultures of two biopsy specimens were negative, as were blood cultures obtained from four patients.

Chemotactic and chemokinetic responses of neutrophils to zymosan-treated serum and to N-formyl-methionyl-leucylphenylalanine were studied as described previously.18 Lymphocyte subpopulations were quantitated by using monoclonal antibodies, and lymphocyte responses to optimum concentrations of phytohemagglutinin, concanavalin A, and pokeweed mitogen were determined by using a conventional lymphoblastoid transformation assay. Skin testing was done by using increasing doses of purified protein derivative of tuberculin (1 to 100 tuberculin units, State Serum Institute, Copenhagen) and Candida albicans antigen (Dermatophytin "O," 1:500 to 1:5, Hollister-Stier, Berkeley, Calif). In Finland, purified protein derivative is applicable to the study of delayed hypersensitivity, as all children are vaccinated with bacille Calmette Guerin.

RESULTS

Based on the clinical and radiologic criteria presented by Björkstén and Boquist, 12 the diagnosis of CRMO was established in eight patients, and the findings were consistent with those of OMG in four patients (Table 1). Two children had a clavicular lesion only.

Clinical Features

Pain in an ankle or knee with or without swelling was the most frequent presenting symptom of both CRMO and OMG (Table 1). Incapacitating back pain with limitation of movement was present for three months in patient 2 before swelling of the clavicular region occurred. Lower

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| | Table 1.—Clinical Data | | |
|-------------------------------------|--|-------------------------|--------------------------|
| Patient No./Sex/ Age at Onset, y | Principal Symptoms at Presentation | Duration of Symptoms, y | Duration of Follow-up, y |
| | Chronic Recurrent Multifocal Osteo | omyelitis | N. S. C. Const. |
| 1/M/9 | Pain and swelling of foot | 1 | 2.5 |
| 2/F/11 | Severe back pain | 4 | 5 |
| 3/F/9 | Knee pain for 1 mo, acute high fever with cramping pains in legs | 4 | 7 |
| 4/F/6 | Pain and swelling of ankle | 7 | 10 |
| 5/F/9 | Low-grade fever, tiredness, "muscle pains," swelling of clavicle | 1 | 2 |
| 6/F/8 | Ankle pain for 2 wk, acute high fever | 1 | 3.5 |
| 7/F/4 | Pain in ankle | 3.5 | 3.5 |
| 8/F/5 | Pain in lumbar region, swelling of ankle | 3 | 3 |
| | Clavicular Osteomyelitis | ALTERNATIVE PROPERTY. | NESSUO KIEN |
| 9/F/13 | Swelling of clavicle | 4 | 6.5 |
| 10/F/10 | Swelling of clavicle | 1 | 2 |
| | Chronic Sclerosing Osteomyelitis | of Garré | |
| 11/M/11 | Pain in knees | 5 | 5 |
| 12/F/9 | Pain in knee | 2 | 2 |
| 13/M/3 | Valgus deformity of knees | 7 | 7 |
| 14/M/7 | Swelling of right leg | 4 | 4 |

back pain coincided with the onset of ankle pain in patient 8. The onset of CRMO was usually insidious, but during the first four weeks of skeletal symptoms, three patients had a short period of fever that was accompanied by cramping "muscle pains" in two of them. Varicella was recorded one month prior to onset in patient 5. Patient 9 had had a candidal infection of the fingernails during the previous year, and an osteitic lesion of the distal III phalanx had been explored four months before the clavicular swelling occurred and C albicans grew. A biopsy specimen from the osteomyelitic clavicle was stained and cultured for C albicans, with negative results.

The clinical picture at onset was suggestive of pauciarticular juvenile rheumatoid arthritis in three patients with CRMO, and patient 11 with OMG

| Table 2.—Location of Bone Lesions | | | | | | | | | | | | | | |
|--|-----|-----|------------|-----|--------------|------|--------|---------|---|-----|-----|----------|-----|---------|
| | | | | | | | Patier | nt No.* | | | | | | |
| Location | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Clavicle | | | | 111 | THE STATE OF | | | | | | | | | |
| R | | R | | R | R | | | | R | | ••• | | | |
| L | | | | | | | | | | R | | | | |
| Humerus | | | | (R) | | | | | | | | | | |
| R | | | | (H) | | 4.16 | | | | | | | | |
| L | | | | | | | | | | ••• | | | | |
| Radius Right proximal | | | | | | | | | | | R | | | |
| Distal | | | | | | | | 7 | | | | | | |
| R | | В | R | | | R | R | | | | | | | |
| L | | | R | | | | | | | | В | | | |
| Left proximal ulna | | В | | 17 | | | | | | | | | | |
| Femur | | | Ly all his | | | | | | | | | | | |
| Right proximal | | | | 5 | | | | | | | В | | | |
| Distal | | | | | | | | | | | | | | |
| R | | | R | | | | | | | | | | R | |
| L | | | (R) | | | | | R | | | | | | |
| Tibia | | | | | | | | | | | | | | |
| Proximal | | | R | R | | | | | | | R | R | | |
| R | | | | | | | 16/21 | | | *** | R | | ••• | • • • • |
| L | | | | R | | | | | | | - | *** | | |
| Distal R | (R) | | | R | | | R | R | | 7 | | | | R |
| | R | | | R | | | | R | | | | | | |
| THE RESERVE OF THE PARTY OF THE | n | ••• | | | | | | | | | | | | |
| Distal fibula R | | | R | | (R) | R | | | | | | | | |
| Ü | | | | R | R | R | R | | | | | A STANKE | | 1 |
| Metatarsals and phalanges | | | | | | | | | | | | | | |
| R R | Rt | | Rt | | | | | (B) | | | | | | |
| L | R‡ | | R§ | 1 | | | | | | | | | | |
| Pelvis | | | | (B) | | | | | | | | | | |
| Total No. of Lesions | 5 | 3 | 10 | 8 | 3 | 3 | 3 | 4 | 1 | 1 | 5 | 1 | 1 | 1 |

^{*}R indicates lesions detected in roentgenograms; parentheses, asymptomatic lesions; and B, lesions detected by bone scan only. †One lesion. \$Three lesions.

had been treated for juvenile rheumatoid arthritis (JRA) for five years before a tibial osteolytic lesion was observed. His symptoms had been mainly nightly joint pains, with occasional mild swelling. Results of antinuclear antibody and rheumatoid factor tests were negative. In the other three patients with OMG, a bone tumor was suspected at referral, on radiologic grounds.

In ten patients new bone lesions developed later, most of them adjacent to the knee or ankle (Table 2). Altogether, the clavicle was involved in five patients, and the small bones of the feet only in three patients. Five patients had back pain and two had chest pain, but in none of them was a corresponding bone lesion verified radiologically, although a bone scan was performed in all patients but one. Exacerbation of the symptoms in previously involved bones was a prominent feature in all patients. In patient 2 the clavicle was reexplored twice because of recurring swelling, heat, and redness, with intense pain. Staphylococcus epidermidis grew from the second biopsy specimen but was considered to be due to contamination.

Pustulosis palmoplantaris was noted in patients 1 and 3, and it coincided with clinical activity of the bone lesions. In patient 4, psoriasis was diagnosed after the bone disease subsided.

Laboratory Findings

The peak erythrocyte sedimentation rates (ESRs) of the patients ranged from 9 to 89 mm/h (mean, 51 mm/h). The C-reactive protein (CRP) levels were below 20 mg/L in eight patients and ranged from 25 to 70 mg/L in five. Clinical activation of CRMO was associated with an increase in ESR above 30 mm/h in all patients but one, but an increase in the CRP level was noted only in two patients. It was probably due to a purulent sinusitis in one. Neither anemia nor leukocytosis was observed, and the serum calcium, phosphorus, and alkaline phosphatase values were normal for age. Serologic studies gave few positive results (Table 3).

| Table 3.—Results of Serologic Tests | | | | | | | | |
|--|-------------------|------|--|--|--|--|--|--|
| Value for No. Positive/ Positive Result No. Tested | | | | | | | | |
| IgM rheumatoid factor | ≥1:128 | 0/9 | | | | | | |
| Antinuclear antibodies | ≥1:20 | 0/9 | | | | | | |
| Antistreptolysin O | ≥200 U/mL | 2/14 | | | | | | |
| Antistaphylolysin | ≥3.2 U/mL | 0/13 | | | | | | |
| Teichoic acid antibodies | ≥1:8 | 0/12 | | | | | | |
| Antibodies to common enteric antigen | ≥1:4096 | 1/10 | | | | | | |
| Yersinia antibodies | ≥1:160 | 0/10 | | | | | | |
| Salmonella antibodies | ≥1:160 | 0/10 | | | | | | |
| Viral antibodies, paired sera | Fourfold increase | 0/3 | | | | | | |

Immunologic Findings

Serum IgG, IgA, and IgM levels were either elevated (IgG in three patients, IgM in one) or normal for age in the 12 patients studied. Complement components C3 and C4 were normal in the 11 patients tested. Neutrophil function was studied in five patients with CRMO (patients 1 through 5), and neutrophil chemotactic and chemokinetic responses to zymosan-treated serum and N-formylmethionyl-leucyl-phenylalanine were normal (84% to 117% of the control cells), as was the chemokinetic activity of the patients' sera (84% to 108% of the control sera). In the four patients studied (patients 1 through 3 and 5), the numbers of T cells, B cells, and subsets of T cells, including T-helper (CD4+) and T-suppressor (CD8+) cells, were all normal, as were the CD4/CD8 ratios. The responses to the mitogens were normal or enhanced in two patients; in patient 3 the response to phytohemagglutinin was 27% of the control, and in patient 1 the response to pokeweed mitogen was 59% of the control, whereas the responses to the two other mitogens were normal in both patients. All seven patients who had skin testing (patients 1 through 5, 7, and 8) reacted to purified protein derivative of tuberculin and/or C albicans.

Radiologic Findings

In patients with CRMO, three to ten bone lesions developed during observation (Table 2). They were initially metaphyseal, well-defined, small osteolytic areas with some sclerosis of the borders (Fig 1). Sclerosis increased during healing but disap-



Fig 1.—Roentgenogram of left knee of patient 3, who had chronic recurrent multifocal osteomyelitis. Osteolytic and slightly sclerotic metaphyseal changes were present three months after onset of symptoms.

peared later. Periosteal new bone formation was seen in metatarsal and clavicular lesions.

In OMG, the initial cystic lesions were surrounded by intensive sclerosis, and there was periosteal new bone formation. When new metaphyseal bone formed it was normal, and the lesions became more diaphyseal with time (Fig 2).

The clavicular lesions mainly affected the medial end of the clavicle and were similar in patients with CRMO and in the two patients with

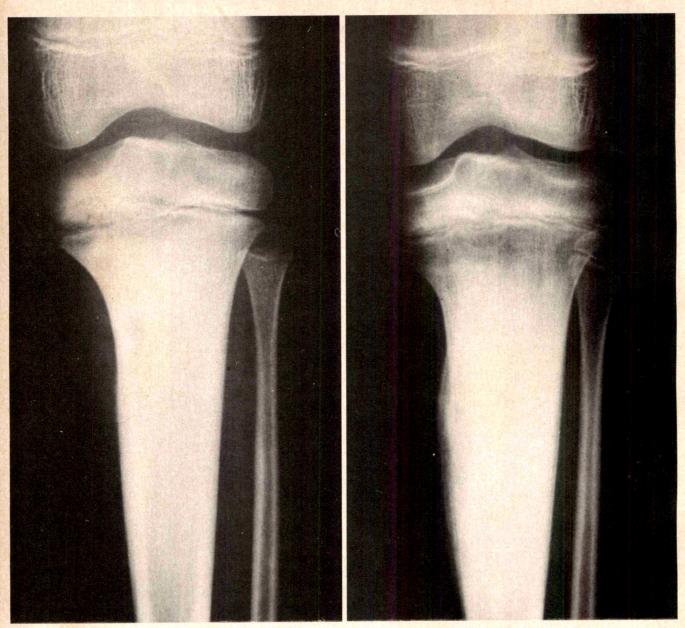


Fig 2.—Left, Roentgenogram of left knee in patient 11, who had osteomyelitis of Garré. Osteolytic areas surrounded by diffuse sclerosis were present in tibial metaphysis. Right, Same lesion 18 months later. Periosteal reaction and intense sclerosis were present in metaphysis except for zone of new bone formation adjacent to epiphyseal plate.

solitary clavicular lesions. Initial lytic lesions were associated with periosteal new bone formation, which in some cases was considerable (Fig 3).

Asymptomatic bone lesions were detected in roentgenograms and bone scans (Table 2).

Histologic Findings

Histologic lesions reflected different stages of chronic, unspecific osteomyelitis. Inflammatory lesions var-

ied from fresh granulation tissue to dense fibrosis. The bone changes were reactive to inflammation. Osteoblasts and osteoclasts associated with bone trabeculi and occasional osteoid formation were present in some cases. A quiescent inflammation with a small number of lymphocytes and plasma cells was the most common lesion. No frank necrosis, granulomas, or specific patterns of inflammation were observed.

Treatment and Outcome

Two patients with OMG were treated with clindamycin hydrochloride for five and 22 months, respectively, following the initial biopsy. In the patient treated for 22 months, a new osteolytic lesion developed at the end of the treatment period. A third patient with OMG received a short course of erythromycin base, and a patient with CRMO received a three-

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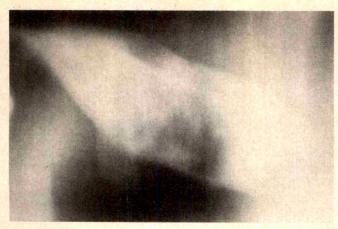




Fig 3.—Left, Tomogram of right clavicle shows lytic changes and sclerotic bone reaction (patient 2). Right, Periosteal new bone formation was present three months later.

Fig 4.—Left, Lytic changes and periosteal reaction of the fourth metatarsal bone in patient with chronic recurrent multifocal osteomyelitis. Right, Premature closure of growth plate and shortening of metatarsal bone were present later.





month course of antituberculous treatment. The other patients were treated with nonsteroidal anti-inflammatory drugs or without drug treatment. Glucocorticoid treatment was not used.

Four patients had complications attributable to bone lesions, and two of them needed corrective surgery. In patient 2, thoracic outlet syndrome developed because of thickening of the clavicle (Fig 3, right). Resection of the first rib was performed, which relieved the symptoms. Patient 9 had similar but more mild symptoms. Patient 3 had growth disturbances of the toes due to premature closure of the epiphyses (Fig 4). Patient 13 fractured his femur while skiing. In patient 14, a marked valgus deformity of the ankle, caused by tibial overgrowth, required osteotomy.

At the end of the observation period, all four patients with OMG were still symptomatic, with recurrences of pain and swelling, in contrast to only two of the eight patients with CRMO.

After follow-up was completed, at the age of 17 years, patient 2 was admitted to another hospital because of severe anemia and proteinuria. A renal biopsy specimen revealed crescents in two thirds of the glomeruli. The right clavicle was reexplored; on histologic examination, no active inflammation was present. She was treated with glucocorticoids, azathioprine, and apheresis. One year later, a biopsy specimen of a pharyngeal tumor showed findings compatible with Wegener's granulomatosis.

COMMENT

Twelve of the 14 patients with chronic osteomyelitislike lesions were considered to have the two described entities, ie, eight patients had CRMO and four had OMG. Distinction between CRMO and OMG was based mainly on radiologic findings, which have been clearly defined in previous reports. 3,9 Clavicular involvement is frequent in CRMO9; one patient with only bilateral clavicular lesions was reported to have CRMO,10 and another with unilateral involvement OMG.3 Therefore, no attempt was made to classify further our two patients who had only clavicular lesions. Sclerotic lesions of the clavicle in children have been reviewed recently.19

The patients for the present series were selected on the basis of radiologic findings suggestive of osteomyelitis and a lack of evidence for a bacterial cause. Routine bacterial cultures do not guarantee that osteomyelitic lesions are noninfectious or even nonbacterial in origin.20 Antibodies to a number of bacterial antigens were measured in the majority of the patients, but few positive results were obtained, and no single pathogen can be suspected on the basis of these results. Previous reports also listed a variety of serologic tests with mostly negative results.8.13,14,17 Elevated antistreptolysin O titers occur in older children with various bone and joint disorders with a frequency that invalidates conclusions about the significance of an elevated value in a single patient.21

Both the ESR, which was elevated in most of our patients and in those reported on earlier, and CRP levels are nonspecific indicators of inflammation. However, CRP levels often can differentiate bacterial from viral infections.²² Notably, elevated CRP concentrations were infrequent in our patients with CRMO, and only occasional positive results have been previously reported. 14,16 Follow-up of our patients disclosed two exacerbations in which an elevated ESR was accompanied by elevated CRP levels, and in one of them a concomitant bacterial infection was present. Thus, CRP levels were not as good as an indicator of disease activity in our patients as has been claimed for patients with chronic staphylococcal osteomyelitis.23

The association of CRMO with pustulosis palmoplantaris, present in two of eight patients, is well documented, 10,15 but the meaning of this association is not known. Infection with varicella and with Candida may have acted as a "triggering agent" for chronic osteomyelitis. It is not clear whether the symptoms noted in some of these patients at onset, such as fever and myalgia, represent manifestations of the causative agent.

Few of our patients received antibiotic treatment, and we could not see any benefit from it. Patients with typical CRMO and OMG—and without

elevated CRP concentrations—can be treated with nonsteroidal anti-inflammatory agents. Severe bone pains in patients with CRMO may be relieved by moderate doses of prednisone. 10,15 This was our observation in two later patients.

The immunologic integrity of patients with chronic osteomyelitis has not been studied very extensively. Serum immunoglobulin levels have invariably been normal or elevated, as in our 12 cases. Depressed skin reactivity to dinitrochlorobenzene and depressed in vitro responsiveness to phytohemagglutinin were found in one of the three patients studied by Björkstén et al. 10 In one patient they found the neutrophil chemotactic responsiveness to be consistently depressed. There is evidence that depressed neutrophil chemotaxis24,25 and inappropriately enhanced chemotactic responsiveness26 can both contribute to the development of inflammatory symptoms. However, our results in five patients with CRMO suggest that, in terms of neutrophil chemotaxis, aberrant inflammatory responsiveness may not play a role in the development of the disease. Blockey27 reported normal leukocyte function test results in a patient with OMG-like bone lesions.27

Chronic recurrent multifocal osteomyelitis has been described as a benign disease that heals without sequelae.9,10 However, we saw complications in patients with CRMO, including overgrowth of the clavicle, leading to thoracic outlet syndrome, and premature closure of metatarsal epiphyses, resulting in growth disturbances of the toes. Probst et al⁹ never observed the latter complication in their 13 patients. In contrast, OMG is known to be deforming; both patients with a distal tibial lesion described by Blockey27 needed a corrective osteotomy, and so did one of our patients.

To our knowledge, the development of Wegener's granulomatosis in a patient with CRMO has not been reported previously. The cause of Wegener's granulomatosis is unknown, but the disease is generally considered a hypersensitivity state. There is no evidence for a triggering agent, but it can be speculated that an uncovered microbe responsible for the bone le-

sions in CRMO could act as one. In Wegener's granulomatosis, bone lesions are apparently very rare. Granulomas have been described in the mastoid bone and cervical vertebrae.28

Three of our patients with OMG and those with clavicular lesions were referred because of possible bone tumor. In patients with CRMO, JRA is often suspected initially. 10,15,16 The lesions of CRMO are only rarely associated with joint effusion.9 On the basis of our

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experience, chronic osteomyelitislike lesions can often be differentiated clinically from synovitis; possible swelling, heat, or tenderness is located somewhat proximal or distal to the joint. Furthermore, morning stiffness is not a feature of chronic osteomyelitis; instead, many patients have joint pains at night or after exertion. Skeletal roentgenograms do not confirm the diagnosis of JRA, but they do exclude other diseases, CRMO among

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them. At early stages, OMG and clavicular osteomyelitis can be differentiated from bone tumor by biopsy only. A biopsy of a solitary lesion is also recommended for microbial cultures to exclude bacterial osteomyelitis and -because we do not know the causes of these two osteomyelitislike diseases -to culture any newly discovered microbes.

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In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

X-linked Congenital Stationary Night Blindness: Review and Report of a Family With Hyperopia

George Khouri, MD; Marilyn B. Mets, MD; Vivianne C. Smith, PhD; Marianne Wendell; Arlene S. Pass (Arch Ophthalmol 1988;106:1417-1422)

Kawasaki Disease and Perineal Rash

Andrew H. Urbach, MD; Robert S. McGregor, MD; J. Jeffery Malatack, MD; J. Carlton Gartner, Jr, MD; Basil J. Zitelli, MD

• During the past several years, we treated seven children with Kawasaki disease who developed a distinctive but rarely described perineal rash. This rash began three to four days from onset of the illness and desquamated in all instances by days 5 to 7. The presence of this rash may facilitate early diagnosis of Kawasaki disease and, hence, may influence the initiation of early treatment.

(AJDC 1988;142:1174-1176)

Since Tomisaku Kawasaki first described the disease bearing his name in Japan in 1967, its diagnosis has depended on a constellation of clinical findings. These include the following: (1) fever, (2) bilateral conjunctival injection, (3) injected pharynx, lips, and "strawberry tongue," (4) peripheral extremity edema and erythema, (5) cervical lymphadenopathy, and (6) polymorphous rash.²⁻⁴ This rash has been described as erythematous, morbilliform, urticarial, scar-

See also p 1136.

latiniform, or erythema multiforme-like.⁵ The predilection of this rash for the perineal area⁶⁻⁸ is often not mentioned in reviews of Kawasaki disease or in pediatric textbooks.^{5,9,10} We believe this rash and its subsequent desquamation are important clinical clues that assist in diagnosis. In light of "incomplete Kawasaki disease" reported by Rowley et al,¹¹ and with potentially new therapies for this entity,¹² accurate early diagnosis takes on added importance. The distinctive

perineal rash with its appearance early in the clinical course of Kawasaki disease may aid in early diagnosis and rapid therapeutic intervention. Seven patients with classic Kawasaki disease are described, each exhibiting a similar perineal rash. The clinical characteristics of this rash and its relationship to other signs and symptoms are also summarized.

Patient Reports

Seven pediatric patients (five girls and two boys) ranging in age from 7 months to 6 years were seen at the Children's Hospital of Pittsburgh over a five-year period. All seven cases conform to Centers for Disease Control's criteria4 for diagnosis of Kawasaki disease. Details of the clinical characteristics of these seven patients are summarized in the Table. All patients were irritable, three of seven had arthralgia or arthritis, in six of seven values for liver function tests were elevated, in four of seven sterile pyuria was present, and peak platelet counts for all patients ranged from 652 to $980 \times 10^{9}/L$. Desquamation occurred in all seven patients; the Figure shows desquamation for patient 7.

COMMENT

The lack of a definitive laboratory test for Kawasaki disease limits the clinician's ability to diagnose this entity with speed and accuracy. The clinician now relies on the well-described features of Kawasaki disease to assist in diagnosis. Formal definition requires a patient to have prolonged fever associated with at least four of the following: (1) conjunctivitis, (2) rash, (3) lymphadenopathy, (4) changes in the oropharynx, and (5) extremity erythema and edema.4 Supportive evidence includes elevated values for liver function tests, arthritis or arthralgia, irritability, cerebrospinal fluid pleocytosis, and sterile pyuria. Despite the importance of these clinical findings for diagnosis, presentation can vary,11.13 and the diagnosis may not be made with confidence until a sharp rise in platelet count, or finger and toe desquamation, or coronary artery aneurysm develops. These three particular findings occur in the second phase of the illness, and, therefore, therapeutic intervention may be delayed.

In addition to the often-described features of Kawasaki disease, each of our patients manifested a rarely discussed but distinctive perineal rash. All seven patients fit the formal case description of Kawasaki disease as outlined by the Centers for Disease Control,4 and they displayed many additional features known to occur with this entity. The perineal rash began as erythematous macules or papules in the perineal area that rapidly progressed to confluence. Within five to seven days of onset of illness the rash desquamated; it always preceded fingertip and toe desquamation by two to six days. The reason for the appearance of this rash in the groin area is not clear; however, the increased trauma, heat, and moisture affecting this area may play a role. Aballi and Bisken⁷ reported the occurrence of this perineal rash in 62.5% (25/40) of their patients, but these authors did not discuss the incidence of desquamation. Conversely, Finks described four patients who developed a maculopapular rash on their extremities, or trunk, or both, with perineal prominence, all of whom eventually showed desquamation of the rash. Hicks and Melish¹⁴ stated that the perineal rash of Kawasaki disease desquamates eight to 15 days after onset of illness.

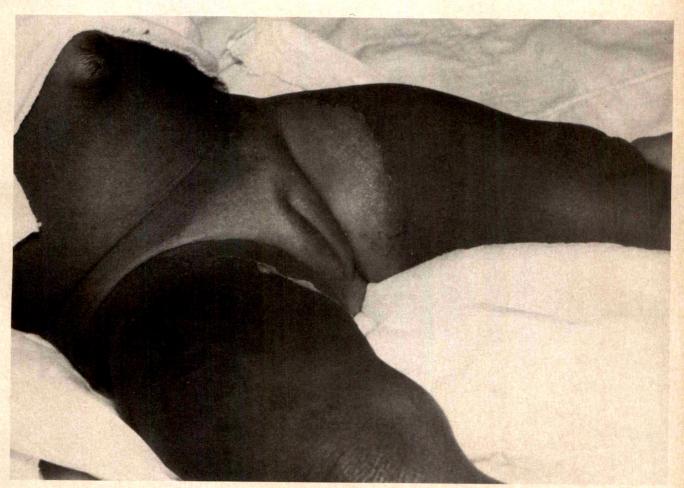
The characteristic appearance of this rash and its predilection for the perineum should be considered a feature of Kawasaki disease. While the differential diagnosis includes drug allergy, toxic epidermal necrolysis,

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| | Kawasaki Disease With Perineal Rash | | | | | | | | |
|--------------------|-------------------------------------|-------------|------------------------|---------------------|----------------------------------|-------------------------|----------------------------------|--------------------------------------|---------|
| | Temperature | ature | Erythematous Mouth/ | | Erythema/ Edema | Day of Finger/ | Characteristics | Perine | al Rash |
| Patient No./Age | Maximum, °C | Duration, d | Cracked Lips | Conjunc- tivitis | of Hands Toe and Feet Peeling | Cervical Lymph Nodes | At Presentation | Day of Desquamation | |
| 1/6 y | 39.5 | 8 | + | + | + | 9 | 3-4 cm anterior cervical | Confluent macular erythema | 7 |
| 2/2½ y | 40.2 | 13 | + | + | + | 13 | 1.5 cm anterior cervical | Confluent macular erythema | 7 |
| 3/2¾ y | 38.9 | 10 | + | + | + | 12 | "Shotty" anterior cervical | Erythematous, pruritic papules | 6 |
| 4/4¾ y | 38.4 | 5* | + | + | + | 9 | "Shotty" posterior cervical | Erythematous, pruritic papules | 7 |
| 5/25/6 y | 40.0 | 14 | + | + | + | 10 | None palpable | Erythematous, pruritic papules | 5 |
| 6/1% y | 40.1 | 12 | + | + | + | 10 | None palpable | Confluent macular erythema | 6 |
| 7/7 mo | 40.2 | 7† | + | + | + | 7† | None palpable | Erythematous papules | 2† |

^{*}High-dose aspirin therapy was initiated on day 5; the patient was afebrile on day 6. †Onset of fever may have been earlier than parent's history suggested.



Desquamative perineal rash in child with Kawasaki disease. Photograph was taken on day 7 of illness.

staphylococcal toxin-mediated syndromes, erythema multiforme, and scarlet fever, the other clinical features of these diseases usually distinguish them from those of Kawasaki disease. The presence of this erythematous perineal rash, especially when desquamation occurs, may be another

supportive feature for the clinician making a diagnosis of Kawasaki disease. The development of this perineal rash, usually on days 3 to 4, with desquamation occurring two to three days later, may hasten the diagnosis and lead to prompt appropriate therapy. In light of the recommended use

of early aspirin therapy, $^{15-17}$ and the possible beneficial effects of prompt γ -globulin treatment, 12,18 we believe this clinical marker of Kawasaki disease may have added importance.

Melinda Suska, Susan Gelnett, Mary Killian, Janice Kelchner, RN, and Nancy Dunn carefully prepared the manuscript.

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In Other AMA Journals

JAMA

Do-Not-Resuscitate Orders

D. J. Murphy (JAMA 1988;260:2098)

Still Needed: A National Academy of Medicine

G. D. Lundberg (JAMA 1988;260:2105)

A NEW LOOK AT FORMULA ALLERGY AND INTOLERANCE: IS SOY EFFECTIVE?

Intestinal closure as an immunologic defense

As one of their many adaptations to the extrauterine environment, formula-fed neonates must also develop the ability to digest and absorb nutrition from ingested infant formula. This is no small task; it includes having to develop physiologic and immunologic defenses against the absorption of any of the more than 25 distinct, potentially allergenic proteins of cow's milk (notably beta-lactoglobulin, alpha-lactalbumin, and bovine serum albumin) or any of the four macromolecular soy proteins (notably glycinin). This maturational process is known as *intestinal closure*.

Breast milk is nutritionally and immunologically ideal, and, except for the occasional presence of intact allergens from the maternal diet, causes no problems for the immature intestinal mucosa. If, however, the infant ingests cow's milk- or soy-based formulas before intestinal closure can occur, the large intact proteins can flatten the villi1.2 and/or cause them to atrophy, increasing the permeability of the lumen and rendering it more vulnerable to penetration by proteins that could provoke systemic or local hypersensitivity reactions. including eczema, asthma, diarrhea, and colic. In addition, episodes of gastroenteritis can damage mucosal surfaces, compromising the effectiveness of the barriers and leading to massive penetration by the allergens.3 This increases the likelihood of further allergic manifestations.4

Early history good for soy protein . . .

Hill and Stuart⁵ first proposed soybean preparations as a substitute for cow's milk in infant formulas in 1929. No allergic reactions to soy were recorded at the time, perhaps due to limited clinical experience, or perhaps because soy allergy may take weeks to develop, making soy-based formulas appear nonallergenic at the outset. In 1960 a series of case reports appeared citing gastro-intestinal and "allergic" reactions to soy protein, followed by additional reports of soy protein intolerance concomitant with cow's milk protein intolerance, and positive intracutaneous tests of soybean protein in allergic children who received soy protein formula in infancy.⁶

... But soy may be as antigenic as cow's milk

Evidence is accumulating that sensitivity to soy is more widespread than was once believed, with estimates averaging around one fourth of infants who are sensitive to cow's milk,^{7,8} but reaching as high as 40%

of these infants.9 Lothe et al10 noted that 53% of colicky infants showed adverse reactions to soy protein formula. May et al11 found that the feeding of soy protein formula from birth to 112 days did not lessen the antibody response to cow's milk protein products fed subsequently. A study by Eastham et al4 also suggests that soy protein may be as antigenic as cow's milk protein. Thus there is evidence that soy protein formula may neither prevent the development of allergies nor resolve symptoms of cow's milk intolerance in many infants, and has been shown to prolong or aggravate these symptoms in some infants. For these reasons the American Academy of Pediatrics Committee on Nutrition (AAP/CON) recommends against the use of soy protein formulas in the dietary management of documented clinical allergic reaction to cow's milk protein, or in the routine management of colic. Instead, AAP/CON recommends protein hydrolysate formulas in these cases.6

Alternatives

Casein hydrolysate formula is hypoallergenic, but its expense (more than twice the price of routine formulas) prohibits routine use. Many parents also report that casein hydrolysate formulas smell and taste unpleasant.

A recently developed whey hydrolysate formula, however, may provide an economical alternative to soy for the management of colic or formula intolerance. As a routine formula, it can delay and may even prevent the development of allergy symptoms in infants at high risk due to a family history of atopy. This hydrolyzed whey protein formula is truly hypoallergenic, moderately priced for long-term or routine use, and has a pleasant taste and aroma. For a monograph on the new product, GOOD START H.A." Iron Fortified Hypoallergenic Infant Formula, write to Carnation Nutritional Products, ACS, 4144 Howard Ave, Kensington, MD 20895.

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Disorders of Higher Cerebral Function in Preschool Children

Second of Two Parts

Isabelle Rapin, MD

AUTISTIC SPECTRUM DISORDERS

Autism is no more a disease than dysphasia or dyslexia, it is a syndrome or symptom-complex of brain dysfunction that may have any one of multiple etiologies (eg, congenital rubella, untreated phenylketonuria, tuberous sclerosis, fragile-X).27 In most cases the etiology is unknown. There are some families in whom it seems to appear as a genetic trait. It affects four boys to every girl. A recent report indicates that autism in some but not all autistic boys without severe mental deficiency is associated with hypoplasia of lobules VI and VII of the cerebellar vermis.28 The significance of this finding remains to be clarified.

The core symptoms of autism, those that make one call a child autistic whatever his IQ, other symptoms, and skills, have to do with affect, socialization and communication, and play (Table 6).29 Therefore, other symptoms, for example, sensorimotor abnormalities, aberrant attention, and mental deficiency, which are seen in some but not all individuals who can be categorized on the autistic spectrum (see below), are concomitants of the core symptoms. Concomitant symptoms presumably reflect nonselective cerebral dysfunction that affects brain systems other than those responsible for core autistic sympAutism is not an "emotional problem," the result of poor parenting, or the result of an emotional trauma. Its pathophysiology is unknown but is hypothesized to be the consequence of abnormal function of cerebral systems required for the experience and expression of drive, affect, and socialization. Autistic children regularly have a communication disorder and cognitive deficits, as well as abnormalities in motor, sensory, attentional, and, in some cases, autonomic function.

Language

The chief complaint of the parents of many autistic children is that of a language disorder. Many autistic children have very delayed acquisition of language, and some remain virtually mute with severely impaired comprehension. Although autistic children may evince a variety of dysphasic syndromes, they all have strikingly impaired pragmatics-the rules for conversational use of language. Mute autistic children typically do not point or attempt to communicate with gestures: many autistic children do not look at their conversational partner (so-called gaze avoidance); others chatter, often with their back turned, without the need for a response. Some speak in overlearned scripts or repeat what they hear verbatim and perseverate rather than engaging in meaningful conversation.

Some autistic children with the semantic-pragmatic syndrome (Table 5 in part 1 of this article) learn to speak early, have good phonologic and syntactic skills, and are verbose. Such children are characteristically echolalic and have a narrow range of conversational topics. Echolalia usually denotes difficulty with comprehension. It is often associated with delayed understanding of the you-me relationship, which results in some autistic children referring to themselves by their name or as you rather than I or me. Immediate echolalia provides extra processing time. Delayed echolalia provides a filler for the child who knows he is supposed to say something but who has difficulty coming up with his own utterance. Perseveration often serves the same function.

Allen²⁹ hypothesized that autistic children suffer from the same language disorders as nonautistic dysphasic children (Table 5 in part 1 of this article), with the exception that purely expressive language disorders (verbal dyspraxia and speech programming disorder) are not seen in autistic children.³⁰ Verbal auditory agnosia and the semantic-pragmatic syndrome are more frequent in autistic than nonautistic dysphasic children.

Cognition

IQ is not a defining feature of the disorder, ie, while, as a group, autistic persons have a lower mean IQ than normal persons, IQ may range from profound mental deficiency to superior intelligence in individual autistic persons. In most autistic children, verbal IQ is lower than performance IQ because of their communication disorder, but there are some children whose verbal IQ is higher; this subsample is referred to by some investigators as Asperger's syndrome.31 Autistic persons are among those with the widest scatter in psychologic subtest scores. This scatter presumably reflects selective neurologic impairment, perhaps associated with anatomic rearrangement in a still plastic brain and, in

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Table 6.—Autistic Symptoms

Core symptoms (always present, severity varies greatly)

Impaired socialization

Inadequately modulated affect

Language disorder always affecting communicative use and comprehension as well as expression

Abnormal play, narrow range of interests

Concomitant symptoms (inconstant, variable severity)

Motor abnormalities, in particular toe walking, stereotypies (eg, flapping, rocking, twiddling, twirling, etc), and oromotor deficits

Sensory abnormalities (increased and/or decreased response to stimuli in the visual, auditory, pain, vestibular, taste, and smell modalities)

Autonomic symptoms, eg, sleep disorders

Aberrant attention (distractible, overfocused, rigidity, tolerance for monotony)

Cognitive abnormalities (level of intellect highly variable, ranging from profound mental deficiency to superior overall ability; great variability in level of competence across skills)

Table 7.—Items in the History Suggesting an Autistic Spectrum Disorder

is aloof or indiscriminately affectionate

While affectionate to family members, is unduly afraid of strangers

is a loner, does not know how to interact with other children, prefers adults to children, tolerates

While he may seek to interact with others, does so ineptly, especially in unstructured social situations

Has a labile affect, unexplained mood swings, and terrors

Is aggressive when unprovoked

Is negativistic, wants everything on his terms

Language was delayed, comprehension is impaired

Has difficulty communicating wants, pointing was absent or appeared late

Has gaze avoidance, turns his back to others

Talks to talk rather than because he has something to say

Verbose, may prefer to talk rather than play, but conversation is limited to a narrow range of favorite topics

Is echolalic, uses verbal scripts, talks to self

Speech is singsong, or monotonous and robotic

Prefers puzzles and mechanical objects to symbolic toys

Has little or no interactive, social, or pretend play

Has overspecialized interests, eg, letters and numbers, maps, timetables, lists, etc

Is rigid in his choice of activities, insists on sameness

Perseverates, has stereotypical compulsive movements (eg, finger flicking, flapping, twirling hair)

Walks on his toes, is clumsy

Has a history of head banging, rocking, self-mutilation

Licks, smells, stares at lights, appears deaf yet is intolerant of loud sound

Has sleep problems

Has an attention deficit or overfocused attention

Has a phenomenal memory for places and routes

Has a phenomenal verbal memory, repeats verbatim

is gifted in some areas (eg, puzzle solving) despite severe deficiency in others

Can read but will not listen to a story or look at pictures

some children, with overfocused attention and extensive practice.

Children with very restricted but hypertrophied skills, such as lightning calculation, knowledge of the calendar, ability to solve a several-hundredpiece puzzle at an early age, in the face of greater or lesser deficiency in other skills, are often referred to as "idiots savants."32 This name is unfortunate because such persons are not idiots because idiocy implies severe overall mental deficiency. Most socalled idiots savants fall within the autistic spectrum. So do most 2-yearolds who are totally engrossed with letters and numbers rather than with

play and with exploring the environment; so are hyperlexic children who learn to read without instruction but whose comprehension is light-years behind their decoding skills; and so are toddlers who recite television commercials verbatim after a few exposures and repeat them to you when you try to engage them in conversation. Although such skills rule out acrossthe-board mental deficiency, they do not predict success in school or in adult life. Children with such skills are among those most deserving of early intervention focused on improving social skills, because some of these children are bright and, with early and

appropriate intervention, they may be able to be put into the mainstream when they reach school age.

Diagnosis

Table 7 lists items in the developmental history that strongly suggest an Autistic Spectrum Disorder. These historical items, especially if many are present, may be more reliable indicators of the presence of autistic traits than observation of the child in the office. This is especially the case in older, less severely affected children, in whom autistic traits are often overlooked but provide a ready explanation for the child's difficult, "weird" behaviors.

In many cases, parents of autistic children recall abnormalities that go back to infancy, such as fussiness ("colic"), sleep disturbances, resistance to cuddling, or, on the contrary, excessive need to be carried around, and unusual tolerance for amusing themselves alone. Some parents report regression in their child's language and social skills, usually during the toddler or early preschool years. after which the child is left severely impaired. The cause of this regression, associated in some children with the development of electroencephalographic abnormalities and a severe receptive disorder for language (acquired epileptic aphasia,33 usually with verbal auditory agnosia), is unknown.

The physician's evaluation of an autistic child must not be limited to the physical and classic neurologic examination, which is unlikely to be specifically abnormal, but must focus on the child's social and communication skills, language and play (see below). There is no test, including blood, cerebrospinal fluid, neuroimaging, and electrophysiologic investigations, to confirm the clinician's diagnostic impression of autism. Because of this, there is considerable controversy among professionals regarding criteria for calling someone autistic. The current view is that there is a spectrum of disorders, ranging from mute, severely retarded withdrawn individuals with motor stereotypies and self-stimulating or self-injurious behaviors to highly intelligent verbose persons with peculiarities such as perseveration, overly rigid social relations and poor ability to make friends, insistence on routines and sameness, a restricted range of activities, and overspecialized interests such as dictionaries, train schedules, and calendars. Many terms have been and are used to describe children with autistic traits, much to the confusion of parents and of some professionals. Some of these include atypical child, pervasive developmental disorder (PDD),³⁴ childhood psychosis, Asperger's syndrome, and nonautistic child with autistic traits or behaviors.

Allen²⁹ hypothesizes that there are distinct syndromes among autistic children, and that one can assign children to these syndromes based on the type of their language disorder, sociability, and play. Other investigators³⁵⁻³⁷ view the disorder as ranging along a continuum of severity, from very mild to very severe, rather than as a syndromic spectrum of disorders.

Autism is not the same condition as schizophrenia, with which it was confused in the past (many autistic children were erroneously called childhood schizophrenics), even though some autistic adolescents may resemble simple schizophrenics. A major difference between autism and schizophrenia is that autism starts in infancy or early childhood and is a static schizophrenia whereas disorder, starts in adolescence or young adulthood and, in most cases, is an episodic disorder, at least in its early stages. Schizophrenia is not as often associated with mental deficiency and with delayed acquisition of language as autism. While hallucinations, especially auditory ones, are characteristic of schizophrenia, they do not, as a rule, occur in autistic children.

Prognosis

Autism usually denotes a static condition. While special education can greatly improve some mildly autistic children's social skills to the point where they are able to attend regular classes, it does not "cure" autism. The children's peculiarities will remain all too obvious to their parents and those who know them well. This is no more grounds for discouragement than in the case of dyslexia: there are many

dyslexic readers; similarly, there are some intelligent autistic persons who improve substantially with appropriate educational intervention even though residual deficits persist lifelong. Although it is said that autistic girls have a worse prognosis than boys, it may be because a number of girls with autistic behaviors are suffering from Rett's syndrome, a recently recognized progressive encephalopathy characterized by hand wringing or licking, lack of head growth, worsening spasticity and ataxia, episodic hyperventilation, profound mental deficiency, and seizures.38

Rutter⁸⁹ states that IQ is the best prognostic indicator in autism. This stands to reason because there is a clear correlation between full-scale IQ and severity of brain dysfunction. Testing autistic children reliably is often difficult and there are many traps in interpreting results of IQ tests in this population, including frequent attention disorders, language disorders, impaired social skills, and negativistic behaviors with poor response to the usual reinforcers.

EVALUATION AND MANAGEMENT OF PRESCHOOLERS WITH INADEQUATE COMMUNICATION SKILLS History

The history indicates whether the child has a problem, the nature of the problem, the probable cause of the problem, and its severity. In addition to focusing on the developmental and past medical histories, particular attention must be given to the family history of language, learning, and psychiatric disorders. With regard to language development, parents are able to provide a rough estimate of how many meaningful words their child produces, eg, less than five, less than ten, less than 20, about 50, too many to count. Parents usually know whether the child uses phrases or short sentences, whether sentence structure is mostly correct, and whether the child is intelligible to family members and to others. One must also ask about comprehension, whether the child obeys simple commands without the need to point or gesture, whether he understands open-ended especially questions,

questions such as "What are you doing?", "Why?", "When?", and "How?" Normal preschool children start to master these questions after they have learned, as toddlers, to answer questions that can be answered by yes or no, and questions about the here and now such as "What's that?", "Who's there?", and "Where is?" A good question to ask the parent is whether the child is willing to listen to stories and can answer questions about them. And, of course, the parents must always be asked about their impression of the child's hearing ability.

It is equally important to ascertain whether the child uses language communicatively, ie, whether he is able to sustain a meaningful conversation, to ask for what he wants, to point, to comment about what is happening. If the child is significantly impaired expressively, does he attempt to use gestures or invent a sign language to get his point across? Severe impairment of language use and lack of drive to communicate suggest autism.

Observation

Physicians are not qualified to evaluate language development quantitatively but, by simple observation, they can often obtain an accurate if rough view of the child's language skills and deficiencies. The most efficient way to do so is to observe the child at play with representational toys, eg, a doll house with little dolls, furniture, cars; to talk to him; and, from time to time, to ask questions about his play. This can be done during history-taking, both as a means of warming up the child and of performing the mental status examination without the child being aware that he is being evaluated. This ploy provides data not only on language development and use but on the child's intellectual level as reflected by his ability to play imaginatively and to pretend. Children who talk to themselves rather than with someone, who talk only about what they want to talk about, who are echolalic or perseverative or speak incessantly without the need for a conversational partner, and who manipulate toys rather than play with them are almost certainly abnormal.

Most pediatricians are familiar with

the Denver Developmental Screening Test,40 a screening instrument for early development. The Early Language Milestones (ELM) Test41 uses the familiar format of the Denver test as a rapid screening instrument, suitable for physicians, which focuses on level of language development. The neurologic standard evaluation, mostly directed at assessing gross sensorimotor function, is rarely revealing; it may disclose mild clumsiness, "soft" motor signs, and oromotor deficits, especially in children whose language deficit is predominantly expressive.30

Referrals

Once the physician has determined that there is indeed a developmental problem, he must refer the child for further assessment. Referral to a multidisciplinary center specializing in the evaluation of a variety of developmental handicaps may be available and is ideal. The following guidelines are provided for pediatricians who do not have access to such a center or who prefer individual referrals.

All children with inadequate language development must have their hearing tested formally and definitively. Screening in the office and a report by the mother that the child hears perfectly is never adequate. Reliable pure tone audiometry is most informative, but if it requires multiple visits to the audiologist or if the child is less than ideally cooperative, is multiply handicapped, or is very young, behavioral testing must be supplemented by brain-stem auditory evoked responses. This test is now widely available, requires no cooperation from the child, and, if necessary, can be carried out while the child is asleep.

A formal speech and language evaluation is required to confirm the impression gained from the pediatrician's informal evaluation by quantitative tests of the different aspects of language.

Psychological or, preferably, neuropsychological testing provides quantitative information about the child's current level of functioning. The IQ is not to be taken as a reliable predictor of later cognitive competence, especially if the child's verbal IQ cannot be assessed or if language-loaded tests such as the old Stanford-Binet or the McCarthy Scales are used. Although nonverbal tests such as the Weschler performance IQ and the Leiter test may be used to rule out mental deficiency, they are less reliable predictors of later success in school and in life than full-scale and even verbal IQ scores. As stated earlier, neuropsychological test profiles provide invaluable information for planning remedial education.

Consultation with a child neurologist well informed about developmental disorders may be useful in severe cases, especially if there is evidence for several developmental disorders. It is also helpful in cases where there is a question of an acquired aphasia, such as a history of regression of early language milestones and deterioration of interpersonal relations that suggest Rett's syndrome38 or acquired epileptic aphasia with verbal auditory agnosia,33 which mandates a sleep electroencephalogram (EEG). Such a history frequently heralds the appearance of overtly autistic behaviors. Determining whether autistic behaviors were present earlier and are only now being recognized or whether they are genuinely new depends on the reliability of the history and on the fortuitous availability of video or audio tape recorded documentation of the child's earlier abilities.

Consultation with a child psychiatrist may be valuable if the physician is uncertain whether behavior disturbances are primary or secondary to the communication disorder. Also, child psychiatrists tend to be aware of therapeutic nurseries that would be appropriate for a child with both a communication disorder and a behavior disorder, whether or not the child is considered autistic. It is important to ascertain that the consultant is a psychiatrist interested in children with organic as well as behavioral problems and one who advocates an eclectic approach to their management. Providing psychotherapy for the parents and play therapy for the child is rarely as effective as referring the child to a specialized preschool and teaching the parents appropriate behavior management (not just behavior

modification) techniques.

Because developmental disorders of higher cerebral function are poorly understood, there is a tendency on the part of some physicians, pushed by the parents' frustration, to perform a variety of tests with a vanishingly low yield. Computed tomographic and magnetic resonance imaging scans are not indicated unless there is evidence for a focal neurologic deficit, nor are routine EEGs except in the case of suspected acquired epileptic aphasia or some other convulsive disorder. A sleep EEG is recommended in autistic children and in those with severe comprehension deficits because seizures occur in up to 25% of autistic children and because some children with severe comprehension deficits may have almost continuous spike and wave EEG discharges during sleep despite the absence of overt clinical seizures.42 Although there are exciting new research tools for assessing cerebral function while subjects are engaged in cognitive tasks, such as computer mapping of brain electrical activity (BEAM), 43,44 of cerebral blood flow, 9 and of metabolism with positron emission tomography (PET),45 these tests have limited clinical application at the present time, especially since the latter two require administration of radioactive compounds.

Unless there is some evidence from the history or the examination pointing to a specific disorder, blood, urine, and other metabolic tests are almost always uninformative. One exception may be chromosome analysis for fragile X syndrome, which may be asymptomatic but is often associated with mental deficiency, attention deficit, autistic traits, and/or dysphasia. 46

Intervention

Referral to a preschool specialized in the education of children with communication disorders is ideal.⁴⁷ Such schools usually provide individual language therapy in addition to the help provided by teachers who emphasize meaningful communication. These preschools are highly beneficial for children with developmental disorders because they encourage independence and appropriate social skills, and supply an enriched environmental ex-

perience and peers who are potent role models for the child. Many also provide guidance for the parents so that there is carryover to the home of what was learned in school. Children with autistic behaviors do best in a therapeutic nursery where attention will be paid to the child's disordered behavior as well as to effective communication. Children with severe comprehension problems, especially verbal auditory agnosia, and those with severe expressive deficits, especially verbal dyspraxia, profit from a program emphasizing alternate communication channels such as total communication (sign language together with speech), communication boards, and early reading instruction.

Less severely affected children may be referred to a preschool for normal children and to a speech and language pathologist for individual language therapy. The physician must emphasize that it is language therapy, not speech therapy, that preschoolers require.

Medication is rarely indicated unless the child is extraordinarily hyperkinetic. Hyperkinesis will often decrease somewhat after the child has a successful school experience and communication skills have improved. Although the *Physician's Desk Reference* does not recommend the use of stimulant drugs such as methylphenidate in preschoolers, prescribing them to children whose hyperkinesis makes it difficult or impossible for them to be retained in school may be justified, keeping in mind that preschoolers may not tolerate this drug as well as schoolage children. The use of phenothiazines in preschool children is rarely indicated.

Autistic preschool children are those for whom the question of medication is most likely to arise. Methylphenidate in low dose may be given a trial. Haloperidol, again in low dose, may have to be prescribed, but one needs to keep in mind that autism is the result of a static encephalopathy and that one must attempt to avoid long-term medication with drugs causing potentially serious side effects or withdrawal problems.

Parent counseling by the primary physician is critical, even though his consultants will also provide advice and information. The pediatrician can synthesize the results of the entire workup and recommendations and transmit them to the parents in a way

that is meaningful to them. Parents have many questions to ask and physicians are best able to answer those about etiology and genetic implications and to discuss medical tests and medications.

Follow-up

It is essential to reevaluate the child from time to time to determine whether intervention is efficacious, whether new problems have arisen, and how much progress the child has made. Reevaluation is most important in the months before entry into kindergarten, since it is at that time that the Committee on the Handicapped in the child's school district will determine whether special education is required, and if so, what type is most suitable. The pediatrician's input to that committee is often decisive.

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Diagnosis of Sjögren's Syndrome in Children

André J. Deprettere, MD; Karel J. Van Acker, MD, PhD; Luc S. De Clerck, MD; Martine K. Docx, MD; Wim J. Stevens, MD, PhD; Hugo P. Van Bever, MD

 We treated four children with clinical symptoms and laboratory findings suggestive of Sjögren's syndrome (SS). We also review the findings in 23 children with the diagnosis of SS whose cases were reported in the literature. We propose that the following criteria for the diagnosis of SS, which are mostly used in adults, should also be applied to children: (1) keratoconjunctivitis evidenced by a Schirmer test and a quantitative rose bengal test; (2) xerostomia shown by a decreased basal and stimulated salivary flow; (3) lymphocytic infiltration in a minor salivary gland biopsy specimen with at least two foci per 4 mm²; (4) laboratory evidence of a systemic autoimmune disorder on the basis of a rheumatoid factor of 1/160 or greater, antinuclear antibody of 1/160 or greater, or extractable nuclear antigen antibodies. Only close observation and longterm follow-up of these patients will allow a better insight in the natural history of SS in children. Those children who do not fulfill these diagnostic criteria also need close and prolonged follow-up study: one of the possibilities is that their conditions will ultimately evolve toward definite SS.

(AJDC 1988;142:1185-1187)

Sjögren's syndrome (SS) is an autoimmune disease that mainly affects the lacrimal and salivary glands, resulting in keratoconjunctivitis sicca and xerostomia. Extraglandular organs, however, may also be involved, giving rise to a multisystem disease.¹ A distinction is made between the primary forms in which no known autoimmune disease such as rheumatoid arthritis or systemic lupus erythematosus can be demonstrated, and the secondary forms of SS in which such association exists.

Sjögren's syndrome has only rarely been described in children. A diversity of diagnostic criteria have been used, and, to our knowledge, no long-term follow-up studies are available.2-13 Before the clinical aspects and the evolution of SS in this age group can be established, agreement must be reached on the diagnostic criteria. In this study we describe four patients with a presumed diagnosis of SS and review the literature on 23 others. The use of well-defined criteria is proposed. The problem of children with minimal or transitory symptoms suggestive of SS who do not fulfill these criteria is also evoked.

PATIENT REPORTS

PATIENT 1.—A girl was first seen at the age of 2 years 7 months with complaints of photophobia since 8 months of age. There were no physical abnormalities except for small stature, pronounced microcephaly, pronounced caries, and bilateral filamentous keratitis. The rose bengal test was positive but, unfortunately, was not scored. Repeated cultures of conjunctival fluid for viral and bacterial agents, including Chlamydia, remained negative. There was no dryness of the mouth. Scintigraphy of the parotid glands with sodium pertechnetate Tc 99m revealed normal uptake but markedly decreased excretion. On bilateral sialography, a stippled accumulation of the dye was seen, compatible with punctate sialadenitis grade 1.14 Echography showed a homogeneously decreased density of both parotid glands. The lesions seen in a lip biopsy specimen consisted of focal dilatation of the ducts and cellular infiltration with plasma cells and lymphocytes: the focus score was 2.15,16 Immunologic investigation revealed negative rheumatoid factor (RF) (nephelometric determination using Behring Laser Nephelometer antisera) and absence of antinuclear antibody (ANA) (immunofluorescence technique

HEp-2 cells as substrate) and anti-extractable nuclear antigen (ENA) antibodies (immunodiffusion technique with thymus tissue as antigen source). Circulating antibodies against submandibular gland tissue (intercellular 1/20 to 1/40; intralobular 1/20 to 1/40) and thyroid microsomes (1/10 to 1/100) were temporarily present. The IgG levels (14.63 g/L; upper normal limit for age, 12.74 g/L) were increased on one occasion. No lupus erythematosus cells could be found. No changes occurred during 2½ years of follow-up.

Patient 2.—A 2-year-old boy had recurrent painless swelling of both parotid glands and no other abnormalities. He had been vaccinated against mumps at the age of 16 months, but no mumps antibodies could be demonstrated at the time of hospital admission. Findings from examination of the eyes were normal; the rose bengal test was negative. Scintigraphy of both parotid glands showed normal uptake and normal excretion. On sialography, the pattern of punctate sialadenitis grade 1 was found. Echography revealed a homogeneously decreased density of both parotid glands. A lip biopsy was performed but contained no salivary gland tissue. The RF, ANA, and anti-ENA antibodies were negative; there were no antibodies against submandibular gland tissue. Serum IgM levels were increased (2.76 g/L; upper normal limit for age, 1.13 g/L). During the following two years, the situation remained unchanged with recurrent enlargement of the parotid glands being the only symptom. The patient was then unavailable for follow-

PATIENT 3.—This boy's history was uneventful until the age of 3 years when he complained of painful swelling of the left parotid gland. Relapses occurred in both glands during the next two years. Findings from clinical examination otherwise remained normal. An eye examination showed normal findings at the age of 5 years 3 months; a rose bengal test was also negative. Scintigraphy of the parotid glands revealed normal uptake and normal excretion. On sialography, punctate sialadenitis grade 2 was found. Echography showed a decreased echodensity of both

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Characteristics of 23 Patients With Diagnosis of Sjögren's Syndrome (SS) Reviewed From the Literature

| | No. of | |
|---|----------|----------------|
| Characteristic | Patients | Reference |
| Clinical symptoms suggestive of SS Parotid gland enlargement | 17 | 2,4,7,9-13 |
| Dryness of the mouth | 15 | 2-6,9,10 |
| Dryness of the eyes | 10 | 3,4,6,12 |
| Symptoms or signs of underlying systemic disease | 12 | 3,4,6,8,10,13 |
| Quantification of keratoconjunctivitis* Rose bengal test | 8/14 | 2~4,8,10 |
| Schirmer test | 14/17 | 2-6,9-11 |
| Tear breakup time | 5/17 | 4 |
| Quantification of reduced salivary flow and parotid lesions* | | |
| Measurement of salivary flow | 6/6 | 2,4,10 |
| Scintigraphy | 7/15 | 2-4,7,9,10 |
| Sialography | 9/10 | 2-4,8-10,12,13 |
| Abnormal result of salivary gland biopsy specimen* | 20/20 | 2-4,6-12 |
| Scored | 8/20 | 4,7 |
| Immunologic investigation* Rheumatoid factor (≥1/160) | 12/19 | 2-4,8-13 |
| Antinuclear antibody (≥1/160) | 17/20 | 2-4,7-9,11-13 |
| Anti-ENA† | 4/13 | 3,4,7,11 |
| Associated autoimmune disease Systemic lupus erythematosus | 5 | 2,7,11,12 |
| Mixed connective tissue disease | 4 | 3,4 |
| Juvenile rheumatoid arthritis | 1 | 6 |
| Progressive systemic sclerosis | 1 | 13 |

^{*}Number of patients with positive results over number of tested patients.

glands. A lip biopsy specimen revealed cellular infiltration but no dilatation of the ducts: a focus score of 1 was given. The RF, ANA, anti-ENA, and antisubmandibularis antibodies were negative. Serum IgM was elevated temporarily (1.84 and 1.64 g/L; upper normal limit for age, 1.00 g/L). Serum levels of C3, C4, and total hemolytic complement were normal. The serologic tests for mumps and human immunodeficiency virus were negative. During the next two years two months, the situation was characterized by periodic enlargement of the parotid glands and an episode of purpuric lesions on the lower legs. At the last examination there were some complaints about irritation of the eyes: results of ophthalmologic examination were normal, however, and a rose bengal test was negative.

PATIENT 4.—A girl was seen initially at the age of 5 years 9 months with biopsyproved leukocytoclastic dermal vasculitis. One month earlier, enlargement of the submandibular glands had been noted. The vasculitis disappeared but on two occasions swelling of the left parotid gland occurred and there were complaints about irritation of the eyes. Results of clinical and ophthalmologic investigation were normal. The

rose bengal test was performed four times and was positive on one occasion with a score of 11.17 A Saxon test18 was repeatedly performed: 1 to 4 g of saliva was obtained. To our knowledge, there are no normal values available in children, but 4 g is above the lower limit found in adults. Scintigraphy of the salivary glands showed normal uptake and normal excretion. On sialography, punctate sialadenitis grade 1 was diagnosed. Echography of both parotid glands was normal. A lip biopsy specimen showed an important cellular lymphocytic infiltration with a focus score of 3 to 4. The RF, anti-ENA, anti-DNA antibodies (immunofluorescence technique using Crithidia luciliae as substrate), and ANA were negative. There were no antibodies against submandibular gland, lupus erythematosus cells were seen on only one occasion, and serum IgM levels were increased (2.21 g/L; upper normal limit for age, 1.00 g/L) as were circulating immune complexes of the IgM type (0.032 g/L; upper normal limit, 0.017 g/L). Serologic tests for human immunodeficiency virus were negative. During the next six months neither the vasculitis nor the parotid swelling recurred, and the immunologic values normalized completely.

REVIEW OF THE LITERATURE

Data on 23 children with cases of SS reported in the literature were collected (Table). The following symptoms suggested the diagnosis: enlargement of the parotid gland, dryness of the mouth, dryness of the eyes, combinations of these symptoms, and clinical or laboratory indications of underlying systemic disease such as arthralgia, Raynaud's phenomenon, vasculitis, and thrombocytopenia. The rose bengal test and the Schirmer test were almost exclusively performed when there were complaints of dry eyes. Scoring of the rose bengal test was exceptional.2,4 Quantitative investigation of the salivary flow and the parotid lesions was mainly restricted to scintigraphy and sialography. Salivary gland biopsy was performed in all but three patients, but the cellular infiltration was scored in only eight of these biopsy specimens. With one exception the authors do not state the criteria for a diagnosis of SS in their patients. A surprisingly high number of associated autoimmune diseases was found in these 23 patients.

COMMENT

In the adult the prevalence of SS approaches or even exceeds that of rheumatoid arthritis.19 Judging from the literature the condition seems to be much more exceptional in children. Furthermore, the available data in children reveal that a diversity of diagnostic criteria have been used and that quantitative investigations have

rarely been performed.

As in the adult, SS should be differentiated from local processes in the eye or the parotid gland, and conditions such as acquired immunodeficiency syndrome, lymphoma, and sarcoidosis should be excluded. The diagnostic criteria proposed by Chudwin et al4 in children have the merit of quantifying the eye and salivary gland involvement, but they include a number of nonspecific signs such as blood cell count, urinalysis, hypergammaglobulinemia, and a positive Coombs' test. They also underestimate the value of anti-SS-A and anti-SS-B antibodies, which are specific of SS. We therefore propose the use of the more stringent criteria that in the adult

[†]ENA indicates extractable nuclear antigen.

have now replaced the criteria of Bloch et al.20 Among these new criteria, those of Fox et al21 have the advantage of being strict and quantitative and of discriminating between primary and secondary forms. They request the fulfillment of all of the following conditions for a certain diagnosis of SS and of three of them for a probable diagnosis: (1) keratoconjunctivitis as evidenced by a Schirmer test and a quantitative rose bengal test; (2) xerostomia as shown by a decreased basal and stimulated salivary flow rate; (3) lymphocytic infiltration in a minor salivary gland biopsy specimen with at least two foci per 4 mm²; and (4) laboratory evidence of a systemic autoimmune disorder on the basis of an RF of 1/160 or greater, an ANA of 1/160 or greater, or ENA antibodies, either anti-SS-A or anti-SS-B. The salivary flow should be evaluated by means of the Saxon test¹⁸ and isotope scanning of the salivary glands. Normal values have to be established for the Saxon test in children. Ultrasonography of the parotid gland may be a valuable noninvasive tool.²² The diagnostic value of sialography with grading of the lesions should be established.¹⁴

When these criteria are used, a definite or probable diagnosis of SS can be made in children. From the four patients described in this report, only one (patient 1) has probable SS. The available data from the literature do not allow such retrospective classification of the 23 patients with presumed SS. It is the careful and prolonged study of the patients who fulfill

these criteria that will provide us with the necessary information on clinical course and evolution of SS in children. In those who do not fulfill the criteria, the diagnosis remains uncertain: one possibility is that they will ultimately develop definite SS, but they may also suffer from other diseases that may be transient (as in patient 4) or permanent. Long-term follow-up is, therefore, equally important in this group. In the patients with isolated parotid swelling, the diagnosis of recurrent parotitis23 should be considered. The identity of this disorder, however, needs confirmation as neither its radiologic nor its histologic features are specific, no eye examinations or immunologic studies are mentioned, and biopsies of salivary glands other than the parotid have not been performed.

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In Other AMA Journals

JAMA

Reuse of Hemodialyzers

M. J. Alter; M. S. Favero; J. K. Miller; P. Coleman; L. A. Bland (JAMA 1988;260:2073)

Cytomegalovirus Infection in a Neonatal Intensive Care Unit

Blood Transfusion Practices and Incidence of Infection

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· We studied blood transfusion variables and cytomegalovirus (CMV) infection in 385 infants admitted to the Duke University Medical Center, Durham, NC, neonatal intensive care unit over 14 months. Cytomegalovirus antibody titers were measured at birth and monthly thereafter. Urine cultures for CMV were performed regularly. Infants admitted in the first six months (n=197) received conventionally prepared blood. Infants admitted in the remaining eight months (n=188) were given frozen, deglycerolized blood. Of the 105 infants weighing 1250 g or less (low birth weight [LBW]), 90 (86%) received transfusions. Two hundred eighty infants weighed more than 1250 g (non-LBW), and 111 (40%) of these were given blood. In the first six months of the study, three infants had

CMV viruria. One case was congenital; two were acquired. Both infants who acquired infection were antibody-positive at birth and received multiple transfusions. In the remaining eight months, five infants had CMV viruria. Two cases were congenital: three were acquired. The three infants who acquired infection were antibody-positive at birth and received multiple transfusions. Our study demonstrates that infants with an LBW are more likely to receive blood transfusion and to be given significantly more blood than non-LBW infants. There was no difference in the number of infants acquiring CMV in the two periods despite the use of different preparations of

(AJDC 1988;142:1188-1193)

Low-birth-weight (LBW) infants frequently develop iatrogenic anemia and may require blood transfusions to replace the blood drawn for laboratory testing. There are few published data to document transfusion usage for LBW infants (1250 g or less) and those who weigh more than 1250 g. The LBW infants, moreover, are at risk for developing life-threatening illness from transfusion-acquired cyto-

megalovirus (CMV) infection, which reportedly occurs in as many as 20% to 30% of seronegative infants. Two studies reported a lower incidence of transfusion-acquired CMV infection with use of frozen, deglycerolized blood, 5 but neither evaluated a control group.

Our study had two purposes: (1) to document blood transfusion practices in LBW and non-LBW (NLBW) infants in an intensive care nursery and (2) to determine the incidence and means of acquisition of CMV infection while using conventionally processed blood or frozen, deglycerolized blood. This study was initiated before the use of frozen red blood cells for neonatal transfusions. Thus, we were able to study sequential admissions without altering the contemporary transfusion practice in the nursery.

PATIENTS AND METHODS Study Population

From July 1984 to September 1985, we studied all infants admitted to the Duke University Medical Center, Durham, NC, neonatal intensive care unit (NICU) within the first week of life. Infants in the NICU at the beginning of the study who were less than 1 week of age were also included. Urine was cultured for CMV on admission, at 4 weeks of age, and weekly thereafter until discharge. In the presence of anuria, saliva was cultured. The CMV antibody titers were determined in cord or infant's blood at birth and monthly until discharge.

Cytomegalovirus status of blood donors was also determined. The amounts and identification for all blood transfusions were recorded. The use of fresh-frozen plasma and platelets was not monitored. All breast milk was heat processed before use.

Infants admitted and who underwent transfusion during the first six months of the study (July to December 1984) were given conventionally prepared red blood cells. Infants admitted to the NICU in the succeeding eight months (January to August 1985) were given frozen, deglycerolized blood.

Figure 1 provides an outline of the study population. At the beginning of the study, 24 infants were in the NICU. Fourteen (six LBW) infants who were older than 1 week of age did not have urine or serologic examinations in the first week of life and had incomplete transfusion data. These infants were followed up with urine cultures and serologic examinations during the study but were not included in the transfusion data analysis. The remaining ten infants were less than 1 week old at the beginning of the study and were included in the analysis. In the first study period, 211 infants were admitted. Ten were older than 1 week of age on admission (nine had

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urine cultures and serologic examinations done) and were not included in the transfusion analysis. Three infants were not tested and were not included in the analysis. The remaining 208 infants form group 1. Of these, 206 had urine cultures, 199 had CMV antibody determinations, and 197 had both.

In the second study period, 244 infants were admitted. Ten (four LBW) infants were older than 1 week of age and were not included in the transfusion analysis. Ten other infants admitted during the absence of the principal investigator were not tested. The remaining 224 infants form group 2. Of these, 220 had urine cultures, 194 had CMV antibody determinations, and 188 had both.

Virus Isolation

Cell culture was performed on a line of human embryonic skin fibroblasts established in our laboratory. Inoculated cultures were observed for cytopathic effects for 30 to 60 days. Isolates were identified as CMVs on the basis of the appearance of characteristic cytopathic effects, the presence of typical inclusions in infected cultures stained with hematoxylin-eosin, and the failure to demonstrate virus replication in epithelial and nonhuman tissue cultures.

CMV Antibody Determinations

Infant and blood donor sera were stored at -20°C before serologic testing. Cytomegalovirus IgG antibody titers were determined using the solid-phase fluorescence immunoassay technique (FIAX, International Diagnostic Technology Inc, Santa Clara, Calif) according to the manufacturer's instructions. Antibody titers higher than 20 were considered positive. Titers of 20 or less were considered negative. Sequential samples from an infant were assessed simultaneously.

CMV Infection

Cytomegalovirus infection was defined as the demonstration of viral shedding in the urine, or seroconversion with rising CMV antibody titers, or a significant rise in antibody titers in infants who were CMV antibody—positive at birth.

Preparation of Red Blood Cells

All blood products used for transfusion to these infants were collected in citrate-phosphate-dextrose-adenine anticoagulant (CPDA-1) and were supplied by the American Red Cross Blood Services based in Charlotte, NC. The customary processing was done using standard methods.

Red blood cell units were frozen according to the high-level glycerol method. The

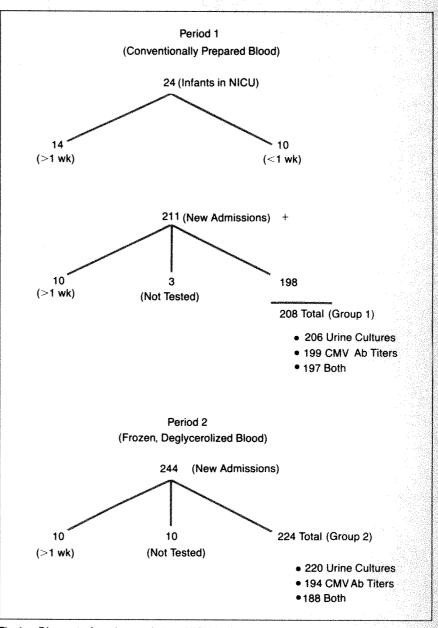


Fig 1.—Diagram of study population. NICU indicates neonatal intensive care unit; CMV, cytomegalovirus; and Ab, antibody.

frozen units were thawed in a heated water bath in accordance with the Standards of the American Association of Blood Banks. Glycerol was removed using cell washer (IBM 2991, IBM Corp, Princeton, NJ). Two 500-mL washes were employed after which the red blood cells were suspended in phosphate-buffered 0.9% saline solution with 0.2% dextrose added. The packed cell volume, or microhematocrit, of the transfused blood ranged between 0.70 and 0.80.

Data Analysis

The χ^2 statistic with the Yates' correction was calculated to analyze the association of birth weight category (LBW or NLBW) with transfusion status (received transfu-

sion or not). The Mann-Whitney rank-sum test was used to compare transfusion variables between groups.

RESULTS Overall Transfusion Variables

In all, 385 infants had urine cultures, serologic examination, and transfusion data available. Of these, 104 were in the nursery for longer than one month (group 1, 39 days; group 2, 65 days), and 82 of these infants received transfusions. Measurements of weight and gestational age for the 385 infants with complete culture, serologic, and transfusion information

were examined (group 1, 197 infants; group 2, 188 infants). Range and mean of birth weight and gestational ages for these infants categorized as LBW or NLBW are given in Table 1, and there were no significant differences between groups. Table 2 shows that a higher proportion of LBW infants (86%) received transfusions than NLBW infants (40%)(P < .001). Infants with a LBW also were given more blood (P < 0.01) from a greater number of donors.

Tables 3 and 4 compare the exposure to blood of infants categorized by study group, birth weight, antibody status, and presence of infection. Transfusion variables for LBW and NLBW infants between groups were not different. In group 1, 36 (78%) of 46 LBW infants received transfusions (median, seven donors; 3.5 antibodypositive; 74 mL of blood, 41 mL of antibody-positive blood) (Table 3) vs 59 (39%) of 151 NLBW infants (median, two donors: one antibody-positive: 56 mL blood: 40 mL of antibodypositive blood) (Table 4). In group 2, 54 (92%) of 59 LBW infants received blood (median, 11.5 donors; 3.5 antibody-positive; 114 mL of blood; 40 mL of antibody-positive blood) (Table 3) compared with 52 (40%) of 129 NLBW infants (median, three donors; 0.5 antibody positive; 68 mL of blood; 7 mL of antibody-positive blood) (Table 4). Two of the CMV antibody-positive LBW infants included in group 2 required exchange transfusions. One of the infants was given three exchange transfusions using frozen, deglycerolized blood and a fourth using conventionally prepared blood (CMV antibody-positive donor). The other infant had two exchange transfusions with conventionally prepared blood (one CMV antibody-positive donor and one CMV antibody-negative donor). Frozen, deglycerolized blood was given for routine transfusions. Neither infant acquired CMV infection.

Incidence of Infections

Four hundred twenty-six (group 1, 206; group 2, 220) of 445 newborns admitted to the NICU during the first week of life had urine cultured for CMV. A total of 961 urine cultures were done, for an average of 2.2 cultures for all infants and 4.5 cultures for LBW infants. Three infants were found to have congenital CMV infection (group 1, one infant; group 2, two infants) and five infants (two in group 1 and three in group 2) acquired CMV infection.

Cytomegalovirus antibody titers were determined for 393 infants

(group 1, 199; group 2, 194). One hundred fifty-one (38%) were seronegative (group 1, 36%; group 2, 41%) and 242 (62%) were seropositive (group 1, 64%; group 2, 59%). The geometric mean titer (GMT) for the seropositive infants was 72 (range, 23 to 400). The GMT for LBW infants was 55. Antibody declined and disappeared in most infants by 8 weeks of age.

Five hundred seven blood donors had CMV antibody determinations. Two hundred thirty-seven (47%) of the donors were CMV seropositive. The GMT was 104 (range, 23 to 400).

Congenital Infections

The overall incidence of congenital CMV infection during the study period was three (0.7%) of 426 infants. One (0.5%) of 206 in group 1 and two (0.9%)of 220 in group 2 were excreting CMV at birth.

Acquired Infections

None of the 147 seronegative infants with urine culture data available had CMV detected in urine during the study period. Five (2%) of the 238 infants with urine cultures available who were CMV antibody-positive at birth acquired an infection (two in group 1 and three in group 2). All infected infants weighed 1200 g or less, were hospitalized longer than one month, and received multiple blood transfusions. Table 3 summarizes transfusion data for infected and noninfected LBW infants.

The two infants in group 1 who acquired CMV infection were given blood from a mean of 14 donors (seven antibody-positive) and with a mean volume of 230 mL of blood (95 mL of antibody-positive blood) (Table 3). The three infants in group 2 who acquired infection received transfusions from a mean of 15.3 donors (5.3 antibodypositive) and with a mean of 147.8 mL

| | Birth Weight, g | Gestational Age, wk |
|-------------------------|-----------------|---------------------|
| Group 1 LBW (n = 46) | 971 ± 167 | 28 ± 1.8 |
| NLBW (n = 151) | 2211 ± 754 | 34.9 ± 3.6 |
| Group 2 LBW (n = 59) | 923 ± 209 | 27.4 ± 2.2 |
| NLBW (n = 129) | 2495 ± 887 | 35.6 ± 4 |
| Total LBW (n = 105) | 944 ± 192 | 27.6±2 |
| NLBW (n = 280) | 2342 ± 818 | 35.2 ± 3.7 |

*See "Patients and Methods" section for explanation of groups. Values are the mean ± 1 SD. LBW indicates low birth weight; NLBW, non-low birth weight.

| Table 2 | .—Comparison of Transfusion | n Variables for Low | r-Birth-Weight (LBW) and No | n-Low-Birth-Weight | (NLBW) Infants* |
|---------|--|---------------------|---------------------------------------|--------------------|--------------------------------|
| Infants | No. Receiving Transfusion/Total No. (% of Total) | No. of Donors | No. of Antibody-Positive Doners | Blood, mL | Antibody-Positive Blood, mL |
| LBW | 90/105 (86) | 9 | 4 | 102 | 43 |
| NLBW | 111/280 (40) | 2† | 1† | 53‡ | 18† |

^{*}Median values are given.

tP<.001.

blood (54.5 mL of antibody-positive blood) (Table 3). When transfusion variables for the five infected infants were compared with transfusion variables for 39 LBW antibody-positive infants who were hospitalized for more than 28 days, there were no significant differences. One of the infants in the second group received transfusion with conventionally prepared blood as well as frozen, deglycerolized blood due to the temporary unavailability of compatible frozen blood.

Figure 2 demonstrates the temporal relationship of CMV antibody status and viruria in the five infected infants. These infants who acquired infection after delivery began shedding virus at 4.5 to 9 weeks of age. Four of the infants had viruria detected in only one urine sample. The only infant who had persistent viruria was delivered by cesarean section and was given only frozen, deglycerolized blood. He began excreting virus at 6 weeks of age and his viruria persisted (11 of 11 urine

samples) throughout three months of hospitalization. His CMV antibody titer two weeks before shedding (1:37) and two weeks after shedding (negative) rose to 1:63 ten weeks after the onset of viruria. When his viruria began, he had been given 152 mL of blood (55 mL of antibody-positive blood) from 16 donors (five antibody-positive; GMT, 187). Three infants were seronegative at the time virus excretion was detected. Two of these infants did not have subsequent anti-

Table 3.—Comparison of Transfusion Variables For Groups 1 and 2 Low-Birth-Weight (LBW) Antibody-Negative (Ab –) and Antibody-Positive (Ab +) Infants*

| | No. Receiving Transfusion/Total | Donors | Ab+ Donors | Blood, mL | Ab + Blood, mL |
|---------------------|------------------------------------|------------------------|-------------------------|-----------|--|
| Group 1 | | AND THE STREET | WAR HOUSE | | SELECTION OF THE PARTY OF THE P |
| LBW | | | | | |
| Ab – Infected | 0 | | | | |
| | | | | | |
| Uninfected | 14/17 | 5 | 3 | 67.5 | 39.5 |
| Ab+ | | | | | |
| Infected-congenital | 1/1 | 1 | | 17.5 | 17.5 |
| Infected-acquired | 2/2 | 14 | 7 | 230 | 95 |
| Uninfected | 19/26 | 8 | 4 | 76 | 46.5 |
| roup 2 | A Company of the Company | NAME OF TAXABLE PARTY. | | | |
| LBW | | | | | |
| Ab – Infected | 0 | | | | |
| | | | | | |
| Uninfected | 24/26 | 12 | 4.5 | 121 | 43 |
| Ab+ | | | | | |
| Infected-congenital | 1/1 | 4 | and the latest the same | 48 | 20 |
| Infected-acquired | 3†/3 | 15.3 | 5.3 | 147.8 | 54.5 |
| Uninfected | 26/29 | 10 | 3 | 107 | 32 |

^{*}Median values are given except for infected infants where mean values are given.

Table 4.—Comparison of Transfusion Values For Groups 1 and 2 Non-Low-Birth-Weight (NLBW) Antibody-Negative (Ab -) and Antibody-Positive (Ab +) Infants*

| | No. Receiving Transfusion/Total | Donors | Ab + Donors | Blood, mL | Ab+ Blood, mL |
|---------------------|------------------------------------|-------------|------------------|---------------|---|
| Group 1 | | 新疆山北 | | | 7.72 |
| NLBW | | | | | |
| Ab – Infected | 0 | | | | |
| | | San Miles | THE PART HE SAME | | |
| Uninfected | 19/55 | 2 | 0.5 | 56 | 6 |
| Ab+ | | | | | |
| Infected | 0 | | | | |
| Uninfected | 40/96 | 2 | 1 | 54 | 28 |
| Group 2 | | | | REPUBLICATION | CANADA PARA PARA PARA PARA PARA PARA PARA P |
| NLBW | | | | | |
| Ab- | | | | | |
| Infected | 0 | T 100 3.9 | | V. Francisco | |
| Uninfected | 15/49 | 4 | 0.5 | 87.5 | 7 |
| Ab+ | | | | | |
| Infected-congenital | 0/1 | | | | |
| Infected-acquired | 0 | | | | |
| Uninfected | 37/79 | 2 | | 45 | 16 |

^{*}Median values are given.

[†]Includes one infant receiving conventionally prepared blood in addition to frozen, deglycerolized blood. See text for explanation.

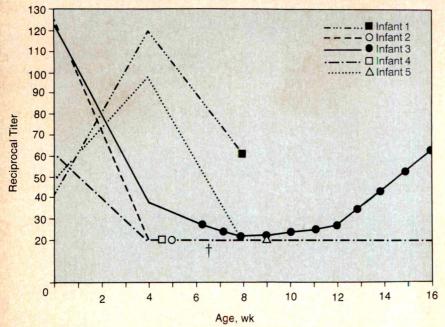


Fig 2.—Relationship of cytomegalovirus titers and viruria in five infected infants. Titers of 20 or less are negative. Dagger indicates death (infant 2). Lines represent titers and symbols represent viruria.

body determinations due to death or discharge from the nursery. One infant, however, who was hospitalized and followed up for three months after the detection of virus in one urine sample (16 cultures done) remained seronegative. This urine was obtained one day after a transfusion with seropositive blood (1:400). The infant who was seropositive when her viruria was detected at 8 weeks of age did not have subsequent antibody determinations or urine cultures done.

Seroconversions

Three infants (one LBW) from group 2 were seronegative at birth with seroconversion after transfusions from seropositive donors (mean, 3.6 antibody-positive donors; GMT, 102; 88 mL of antibody-positive blood). Urine cultures for these three infants remained negative. Two to three cultures per infant were obtained from birth to 4 to 8 weeks of age. One of the infants had three antibody titers (negative, 1:58, 1:31) done at birth and at 4 and 8 weeks of age, respectively. The remaining two infants had only two antibody titers each (negative, 1:56; negative, 1:52) done at birth and 4 weeks of age. Blood for the antibody determination was obtained at four to 12 days after the infant's most recent transfusion. All infants were given frozen, deglycerolized blood and one infant was given fresh-frozen plasma. These infants were not included in the group of infants with culture confirmation of infection.

COMMENT

There were two important findings from our study. First, LBW infants were given blood transfusions more frequently and consequently were given blood from a larger number of donors and in larger volume than NLBW infants. Second, the incidence of acquired CMV infection was very low in our population and did not differ in the two groups despite the use of different preparations of blood.

Transfusion Variables

Our data show that 86% of LBW infants received transfusions compared with only 40% of NLBW infants. Infants with an LBW also were given more blood from a greater number of donors than NLBW infants. This is to be expected because LBW infants are frequently very ill and require prolonged intensive care. 8.9 Our data confirm that LBW infants are given large amounts of blood, up to six times the circulating blood volume, making this

group of infants at greater risk for acquiring a blood-borne infection.

CMV Infections

The overall incidence of CMV excretion during the study period was 1.9%, and 5.8% for infants hospitalized for longer than one month. The rate of infection, however, among CMV antibody-negative infants given conventionally prepared blood was zero. This finding differs from previous studies in which LBW CMV antibody-negative infants were at a 20% to 30% risk for acquiring infection from transfuof CMV antibody-positive blood.1-3 Our data may be limited by the small number of LBW antibodynegative infants who were given conventionally prepared blood. Also, these infants, by chance, were given blood from fewer donors and fewer antibody-positive donors than LBW infants in other studies assessing transfusion-transmitted CMV.2,3 We had 14 antibody-negative LBW infants given a median of 39.5 mL of conventionally prepared blood from a median of three antibody-positive donors. Other investigators have found an increased incidence of transfusion-acquired infection in infants given blood from a mean of 6.5 CMV antibodypositive donors or greater than 50 mL of antibody-positive blood. 2,3 Seroconversion did not occur in these 14 infants, so we believe that the negative cultures were not indicative of a failure to detect virus.

Five infants acquired CMV infection. All of these infants were LBW, were antibody-positive at birth, received multiple blood transfusions, and were hospitalized for longer than one month. Comparison of transfusion variables for the five infected infants and 39 LBW antibody-positive infants hospitalized for more than 28 days revealed no significant differences. All newborns who excreted CMV after the first week of life were initially seropositive, making it possible that they acquired virus perinatally from their mothers. Three of the five infants excreted virus at 4.5, 5, and 6 weeks of age, respectively, and it was not possible to determine the source of their virus. Two infants excreted virus at 8 and 9 weeks of age, respectively. These infants seem less likely to have

acquired their viruses from their mothers. Virus isolations were not attempted from mothers and therefore no comparisons of the isolated viruses could be made. Also, because platelet transfusions were not monitored, we cannot exclude that as a possible source of infection.

Three of the five infants were seronegative and another had a very low antibody titer when virus was detected in the urine. One infant died 1.5 weeks after virus was isolated. Four infants had virus detected in only a single urine sample. The one infant who had persistent viruria was seronegative two weeks after the onset of viral shedding but was seropositive four weeks later. One infant remained seropositive from birth to 2 months of age, documenting her acquisition of virus and infection. One infant failed to seroconvert in three months of observation. Thus, several interesting observations have been made. Seroconversion by immunofluorescence may not be detected for months after infection. Transient or possibly sporadic excretion occurs, and we need to learn more about the significance of this finding.

Three infants from group 2 who were seronegative at birth became seropositive during their hospitalization. All received transfusions with frozen, deglycerolized blood. All urine cultures were negative. One infant had a declining antibody titer on followup, suggesting passively acquired antibody and not infection. The remaining infants had insufficient data to allow

conclusions concerning their seroconversions. Therefore, these infants are not included as infected infants.

We could not demonstrate a difference in the incidence of acquired CMV infection between the infants receiving conventionally prepared blood and those who received frozen, deglycerolized blood. This study, however, may be affected by the number of LBW CMV antibody-negative infants given transfusions, the number of antibody-positive donors per infant, the amount of antibody-positive blood transfused, and the lack of long-term follow-up in infants hospitalized for less than one month.

Other studies assessing the effectiveness of frozen, deglycerolized blood have also been limited by small numbers of infants as well as the lack of internal controls.4.5 Brady et al4 found that none of 106 seronegative infants (27 LBW) receiving transfusions from a mean of 5.7 U of frozen, deglycerolized blood (half from seropositive donors) acquired CMV.4 Taylor et al⁵ found that none of 17 LBW seronegative infants who were given only frozen, deglycerolized blood acquired CMV infection, while two of seven LBW seronegative infants given both conventionally prepared blood and frozen, deglycerolized blood acquired CMV.5

While frozen, deglycerolized blood appears to be effective in preventing transfusion-acquired CMV infection, there may be complications associated with its use. Recently, an increase in serum bilirubin levels temporally as-

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sociated with transfusion of frozen, deglycerolized blood was mentioned as an unpublished observation.⁵ An infant in our series, after being given a double-volume exchange transfusion using frozen, deglycerolized blood, developed severe metabolic acidosis. He had two subsequent exchange transfusions using frozen, deglycerolized blood, with metabolic acidosis occurring after each. A fourth exchange transfusion performed using conventionally prepared blood produced no ill effects. Following this, we chose to carry out exchange transfusions with conventionally prepared blood and to use frozen, deglycerolized blood for routine blood replacement when smaller volumes are transfused. Further experience with frozen, deglycerolized blood is necessary to determine possible complications from its use.

In summary, we found that 86% of LBW infants are transfused from a median of nine donors, putting them at risk for a transfusion-transmitted infection. In this study, only CMV antibody-positive infants became infected with CMV. Finally, the incidence of acquired CMV infection was very low in our population and did not differ in the two groups despite the use of different preparations of blood.

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Quotables:

New Medicines: I always use the newest medicines quickly before their effectiveness runs out.

SIR WILLIAM OSLER Perspectives in Biology and Medicine 1985

Taurine and Osmoregulation

II. Administration of Taurine Analogues Affords Cerebral Osmoprotection During Chronic Hypernatremic Dehydration

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• We have previously shown that in the cat, taurine is an osmoprotective molecule that lessens mortality, neurological morbidity, and brain-cell dehydration during chronic hypernatremic dehydration. We examined the ability of two taurine analogues to afford cerebral osmoprotection in rats. Pretreatment with guanidinoethane sulfonate, a competitive antagonist for B-amino acid transport, as a 1% drinking solution for ten days led to a significant reduction in brain-cell dehydration. Thus, total braincell water was higher in experimental vs (544.3 ± 36.8) control animals 478.2 ± 12.7 mL/100 g of fat-free dry sol-Ids [FFDS]) and the difference was almost exclusively derived from the intracellular water compartment (452.7 ± 27.3 vs 371.4 ± 7.7 mL/100 g of FFDS). Pretreatment with taltrimide, a lipophilic taurine derivative (intraperitoneal injection of 200 mg/kg for four days), led to similar results. Total brain-tissue water was significantly higher in experimental vs control rats (507.6 ± 18.8) 363.2 ± 9.5 mL/100 g of FFDS), with the difference primarily derived from the intracellular water space (372.8 ± 18.1 vs 221.3 ± 13.1 mL/100 g of FFDS). These results suggest that the cerebral response to chronic hypertonic stress includes accelerated transmembrane flux of osmoprotective solutes in addition to mobilization from sequestered intracellular storage sites in an attempt to increase the cytosolic pool of osmotically active molecules.

(AJDC 1988;142:1194-1198)

Cell-volume regulation in response to alterations in ambient osmolality is an important biologic function in all animal species.1,2 In mammals, osmoprotection is primarily designed to maintain cerebral-cell volume relatively constant in the face of disturbances in serum tonicity.3 We have shown that taurine acts as an osmoprotective molecule in the cat and is instrumental in the defense against brain dehydration during ehronic hypernatremic dehydration(CHD).4 Therefore, we thought it worthwhile to explore the potentially beneficial effect of taurine analogues in rats with

Investigations into the osmoregulatory role of taurine and structural analogues may have clinical relevance to the human infant with a limited capacity for taurine biosynthesis. Recent studies have indicated that neonates fed commercial formula without taurine supplementation may develop metabolic evidence of taurine deficiency.⁵ In addition, infants treated with hyperalimentation solutions for prolonged periods manifest abnormal retinograms that are indicative of target organ injury due to taurine deficiency.6 In light of the frequency of osmolal disturbances in the ill neonate,7 a better understanding of the function of taurine in cell-volume regulation may improve the therapy for infants with hypernatremic or hyponatremic syndrome.

Guanidinoethane sulfonic acid (GES), also known as taurocyamine, is structurally related to taurine and competes with taurine for transport in brain-derived synaptosomes.8 We anticipated that pretreatment of rats with GES would lead to cerebral-cell taurine depletion and enhance the deleterious consequences of CHD in a manner similar to dietary taurine deficiency in the cat. In contrast, prior administration of taltrimide, 2-phthalimidoethanesulfon-N-isopropylamide, should increase the effective cerebral cytosolic taurine concentration since it is more lipophilic and penetrates the blood-brain barrier with greater efficiency compared with taurine.9 Therefore, we expected taltrimide to provide osmoprotection during CHD. The following experiments describe the impact of pretreatment of rats with these two novel compounds on their tolerance of CHD.

METHODS

Sprague-Dawley rats weighing 179 to 383 g were used in these experiments. They were fed a standard rodent diet (ICN Biochemicals, Cleveland) containing 20% protein (casein-purified high nitrogen), but no taurine for two to four weeks to ensure that all tissue taurine content was endogenously synthesized and not derived from the diet. Animals were weighed weekly and then studied in two protocols.

In protocol 1, experimental animals (n=16) received GES dissolved as a 1% solution in their drinking water for 14 days. 10 Control animals were provided untreated water ad libitum. After two weeks, the animals were weighed and blood was drawn for serum chemical and plasma tau-

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Huxtable); and Health Sciences Center at Brooklyn, SUNY at Brooklyn (Dr Finberg).

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Reprint requests to the Division of Nephrology, Schneider Children's Hospital, New Hyde Park, NY 11042 (Dr Trachtman). rine concentration analyses. Chronic hypernatremic dehydration was induced by complete water deprivation for 24 hours. This was followed by twice daily intraperitoneal injections of 1 mol/L of sodium chloride over 72 hours in an effort to gradually raise serum Na+ concentration to 185 to 190 mmol/L.11 The daily dose in milliequivalents, which was equivalent to the injected volume, was calculated according to the following formula: milliequivalents = $0.6 \times (total body weight) \times (desired)$ serum Na+-140). Animals were weighed daily and blood was drawn at the time of death for final determination of serum Na+ and Cl concentrations. The animals were dissected and a portion of the vastus medialis muscle and brain tissue from the frontal lobe were removed for measurement of tissue water content, water compartment sizes, and taurine content.

In protocol 2, experimental animals (n=12) received taltrimide dissolved in 0.15 mmol/L of sodium chloride, 200 mg/kg/d, injected intraperitoneally for four days. Control animals were given an equal volume of saline vehicle by the same route.

Thereafter, CHD was induced and samples were collected as described in protocol 1.

Analytical Methods

Serum and tissue chemical analyses for Na+ and K+ were performed using a flame photometer (Instrumentation Laboratories, Lexington, Mass) while serum and tissue chloride concentrations were measured with a Buchler-Cotlove automatic titrator chloridometer (Haake-Buchler Inc. Saddle Brook, NJ). The brain and muscle tissue specimens were dried to constant weight in an oven at 40°C for determination of percentage water content.11,12 The specimens were then extracted once with ether and redried to constant weight. The tissues were digested in 1 mL of 70% nitric acid solution for 48 hours and the extracts were then neutralized with calcium carbonate. The brain and muscle tissue samples used for determination of taurine concentration were homogenized in nine volumes of cold 10% trichloroacetic acid using a Polytron homogenizer (Brinkman Instruments, Westbury, NY) and centrifuged at 20 000 g for 30 minutes. The plasma and tissue taurine content was measured with an automated amino acid analyzer (Beckman Instruments, Fullerton, Calif) on-line to a computer (Spectra Physics, Oxnard, Calif) for data acquisition and calculation. The GES concentrations in the tested organs were determined as described by Huxtable et al. 13

Table 1.—Chronic Hypernatremic Dehydration*

| | | Results by Tre | eatment Group | |
|---|----------------------------|------------------------|------------------------|-------------------------|
| | G | ES | Taltrimide | |
| Criteria | Control (n=8) | Experimental (n = 8) | Control (n=7) | Experimental (n = 5) |
| Weight, g Predehydration | 312.0 ± 14.2 | 314.3±9.4 | 413.7 ± 17.5 | 410.6 ± 14.0 |
| Postdehydration | 258.5 ± 10.5† | 255.5 ± 12.4† | 344.0 ± 17.8† | 345.0 ± 21.0† |
| Serum NA+ level, mmol/L Predehydration | 142.4±0.7 | 141.3±0.7 | 136.9±1.6 | 135.2±1.6 |
| Predehydration plasma taurine level, μmol/L | 202.1 ± 3.8† 29.1 ± 5.9 | 198.3±3.0† 22.1±4.7 | 183.4±2.9† 31.3±5.4 | 186.0 ± 1.4† 47.5 ± 6.3 |
| Mortality | 5/8 | 2/8 | 1/7 | 0/5 |

^{*}GES indicates guanidinoethane sulfonic acid. Results are mean \pm SEM. †P<.01, predehydration vs postdehydration.

| Table 2.—Cerebral Water Compartment Sizes* | | | | |
|--|---|---------------------------|---------|--|
| | Cerebral Water Compartment Sizes, mL/100g of FF | | | |
| Treatment Group | TTW | ICW | ECW | |
| GES | | P. C. Carlotte | | |
| Control (n = 8) | 478 ± 13 | 371 ± 8 | 107±9 | |
| Experimental (n = 5) | 544 ± 37 | 453 ± 27† | 91 ± 7 | |
| Taltrimide | | THE STATE OF THE STATE OF | | |
| Control (n = 7) | 363 ± 10 | 221 ± 13 | 142±8 | |
| Experimental (n = 5) | 508 ± 19‡ | 373 ± 18± | 135 ± 6 | |

^{*}FFDS indicates fat-free dry solids; TTW, total tissue water; ICW, intracellular water; ECW, extracellular water; and GES, guanidinoethane sulfonic acid. Results are mean ± SEM.

Calculations

The extracellular water (ECW) of the tissue samples was calculated as the chloride space. 12 The latter was determined by dividing the tissue chloride content by the serum chloride concentration corrected by the Donnan factor (0.96) and for the water content of plasma (0.93). The intracellular water (ICW) content was derived as equal to the total tissue water (TTW) content minus the ECW component.

Statistical Methods

The results were analyzed using the Student t test, paired or unpaired, as indicated by the experimental conditions. Results were considered statistically significant if P < .05

RESULTS

In both protocols, the animals thrived and gained weight on the taurine-free diet and during the pretreatment phase with the taurine analogues. As indicated in Table 1, the degree of weight loss was comparable in the experimental and control ani-

mals treated according to the two protocols. Although the GES-treated rats and their control counterparts had more severe hypernatremia than the taltrimide-treated rats and their respective controls, the severity of the CHD regimen was comparable among the animals in each protocol. The older age and larger body size of the animals studied in protocol 2 may have facilitated the natriuretic response to the long-term sodium loading. There was a trend toward increased mortality in the control animals (five of eight) compared with rats that received GES in their drinking water (two of eight), but this difference was not statistically significant. No substantial animal mortality was observed in the taltrimide study. Furthermore, no evident seizure activity was seen in any of the animals with CHD that were treated according to these two protocols. However, in both studies the control animals had a sicker, more lethargic appearance, with disheveled fur, com-

[†]P<.05, experimental vs control ‡P<.005, experimental vs control.

pared with experimental rats pretreated with taurine analogues.

In both experimental studies, treatment with the taurine analogues, either GES or taltrimide, provided significant protection against brain-cell desiccation during sustained hypertonicity. As indicated in Table 2 and Figs 1 and 2, animals that received GES compared with those that received normal drinking water had an increase in brain TTW (544 ± 37 vs 478 ± 13 mL/100 g of fat-free dry solids [FFDS], P = .15) that manifested as a preservation of the ICW compartment $(453 \pm 27 \text{ vs } 371 \pm 8 \text{ mL}/100 \text{ g of FFDS},$ P<.05). A similar pattern was also observed in protocol 2. Animals that were pretreated with taltrimide had a significantly increased brain TTW compared with control animals $(508 \pm 19 \text{ vs } 363 \pm 10 \text{ mL/}100 \text{ g of})$ FFDS, P<.0001) that was due to maintenance of the ICW compartment size $(373 \pm 18 \text{ vs } 221 \pm 13 \text{ mL/}100 \text{ g of}$ FFDS, P < .001). The smaller cerebraltissue water compartment sizes in the control animals studied as part of the taltrimide vs GES protocol may be attributable to older age and longer survival in the taltrimide-pretreated animals, and differences in lipid extraction in dried tissue samples. No differences in muscle-tissue water compartment sizes were noted between animals pretreated with GES or taltrimide and their appropriate controls. This is consistent with our previous observation that taurine did not display an osmoprotective function in muscle tissue of cats during CHD.4

In protocol 1, while no difference in plasma taurine concentration was demonstrable, there was a 22.6% decrease in cerebral taurine content in the rats that were given GES in their drinking water during the preparatory phase (Table 3). However, this was significantly less than the 38.1% reduction in muscle taurine content induced by pretreatment GES. Furthermore, GES pretreatment caused a substantial increase in the GES content of the brain $(1.23 \pm 0.09$ [experimental animals] vs 0.58 ± 0.05 mmol/L/100 g of FFDS [control animals], P < .0001). Thus, the total cerebral content of taurinelike molecules was similar in the control

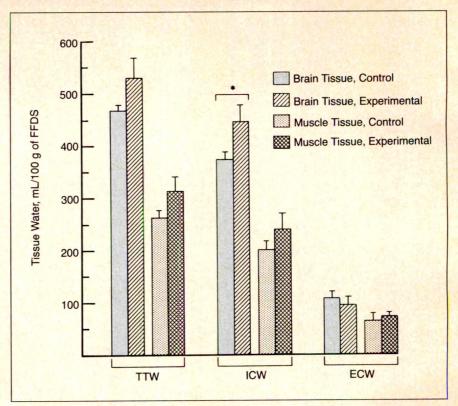


Fig 1.—Graph illustrates brain and muscle tissue water compartment sizes in rats with chronic hypernatremic dehydration. Experimental animals (n=8) were pretreated with guanidinoethane sulfonic acid as 1% drinking solution while control animals (n=8) received untreated water. TTW indicates total tissue water; ICW, intracellular water; ECW, extracellular water; FFDS, fat-free dry solids; and asterisk, P < .005.

| | Taurine Concentration by Tissue, mmol/L/100 g of FFDS | | |
|----------------------|---|-----------------|--|
| Treatment Group | Brain | Muscle | |
| GES | 的 机会发展,这个特别的是一个 | | |
| Control (n = 8) | 2.75 ± 0.23 | 3.78 ± 0.46 | |
| Experimental (n = 8) | 2.13 ± 0.15† | 2.34 ± 0.271 | |
| Taltrimide | | | |
| Control (n = 7) | 1.18 ± 0.29 | 4.19 ± 0.27 | |
| Experimental (n = 5) | 2.56 ± 0.30‡ | 3.61 ± 0.30 | |

*FFDS indicates fat-free dry solids; GES, guanidinoethane sulfonic acid. Results are mean ± SEM. †P<.05, experimental vs control. ‡P<.01, experimental vs control.

and experimental animals $(3.33\pm0.28$ vs 3.36 ± 0.41 mmol/L/100 g of FFDS, respectively). In the second study, taltrimide treatment resulted in a 217% increase in cerebral taurine content $(2.56\pm0.30$ vs 1.18 ± 0.29 mmol/L/100 g of FFDS, P<.01), without causing any concomitant change in muscle taurine content.

COMMENT

Our results demonstrate that prior treatment with two distinct taurine

analogues ameliorates cerebral dehydration and lessens the morbidity observed in rats with CHD. In earlier work we demonstrated the importance of taurine in cerebral-cell volume regulation by describing the increased morbidity, mortality, and extent of brain-cell shrinkage during CHD in cats with dietary taurine deficiency.⁴ Since the cat has a marginal taurine biosynthetic capability^{14,15} and utilizes taurine as an obligate bile salt conju-

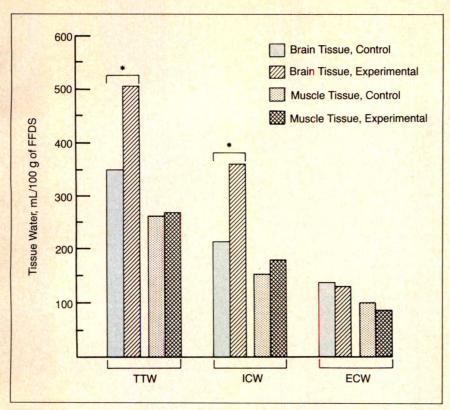


Fig 2.—Graph illustrates brain and muscle tissue water compartment sizes in rats with chronic hypernatremic dehydration. Experimental animals (n=5) received intraperitoneal taltrimide (200 mg/kg/d for four days) while control animals (n=7) were given saline injections. TTW indicates total tissue water; ICW, intracellular water; ECW, extracellular water; FFDS, fat-free dry solids; and asterisk, P<.005.

gate, ¹⁶ eight to 12 weeks of taurine deprivation leads to an 80% reduction in cerebral taurine content. ¹⁷ Depletion of brain taurine concentration correlates with the degree of cerebralcell dehydration during CHD. ⁴ The rat, in contrast, has ample activity of all enzymes required for taurine synthesis in muscle, liver, and brain tissue. ¹⁸

Thus, it is not feasible to induce taurine deficiency by excluding this sulfur amino acid from the diet. Instead, we sought to modify brain taurine content with exogenous administration of taurine analogues. Our results indicate that such a strategy can change the susceptibility to CHD. In particular, using the two analogues tested, we successfully increased the animals' tolerance to CHD and reduced cerebral-cell volume shrinkage during a sustained hyperosmolar state.

It is important to emphasize that our conclusions are based on the relative differences in cerebral water com-

partment sizes in experimental vs control animals. Thus, the absolute value of differences in brain water compartment sizes in different animal groups or compared with normal, untreated animals is less important than the directional change induced by prior administration of GES or taltrimide compared with simultaneously studied control rats. Since the precise anatomic meaning of the brain chloride space is a matter of dispute, we think that an interpretation of the data based on relative changes in brain water compartment sizes following experimental interventions is justified. The muscle-tissue water compartment sizes were similar in all four groups of rats studied and no differences in these values were detected between experimental and control animals.

Guanidinoethane sulfonic acid is an amidine analogue of taurine that acts as a competitive antagonist of tissue taurine uptake. 8,10 Its administration as a 1% drinking solution for ten to 14 days causes a 40% to 60% decrease in

cerebral taurine content. Thus, the observation that GES pretreatment afforded cerebral osmoprotection during CHD was unexpected. This is especially surprising since intracisternal administration of GES lowers the seizure threshold in normal rats.19 However, in our experiments, GES induced only a 22.6% reduction in cerebral taurine content. This suggests that CHD interfered with the ability of GES to deplete the brain of taurine. In addition, GES is transported into the brain cell by the same \(\beta\)-amino acid carrier system as taurine and shares some agonist properties with taurine.8,20 Therefore, it is possible that the protective effect of GES was mediated by an increase in the pool of available, active taurinelike molecules in the cerebral cytosol. The beneficial effect of taltrimide is easier to explain. It is likely that this lipophilic molecule penetrated the blood-brain barrier better than taurine and entered the cerebral cell during the pretreatment phase.6 This may have led to an increased number of taurinelike molecules in the intracellular pool of osmoprotective organic solutes. This proposed mechanism of action is supported by the significantly elevated brain taurine content in the experimentally pretreated animals in protocol 2. While we have focused on a potential osmoprotective role of taurine analogues by supplementing the cytosolic pool of osmolytes, these molecules may be working by alternative mechanisms. These could include maintenance of endothelial membrane ultrastructure and limitation of water egress from the brain during CHD. Taurine exerts such a protective effect of pulmonary epithelial integrity during nitrogen dioxide exposure.21

In these experiments, in contrast to our previous studies of osmoregulation in cats, no differences in mortality were demonstrable between the experimental and control animals, despite a significant reduction in braincell dehydration in the rats pretreated with taurine analogues. This may be a consequence of increased resilience of the rat to experimental manipulation and differences in endogenous taurine biosynthesis. ¹⁵ Thus, a protective effect of pretreatment with taurine an-

alogues on mortality may have been obscured by the retained ability of control rats to synthesize taurine in the brain. However, in both protocols, the control animals had a sicker, more lethargic appearance, with disheveled fur, compared with experimental animals. This supports the contention that pretreatment with taurine analogues had a beneficial effect.

All previous discussions of organic osmoprotective molecules in mammalian species have assumed that an increase in their cytosolic concentration in response to a rise in the osmolality of the extracellular fluid would be derived from intracellular sequestration sites.^{2,3} It is postulated that increases in ambient tonicity signal a release of endogenous taurine and other osmolytes from unidentified

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Quotables:

Stealing: If you steal from one author, it's plagiarism; if you steal from many, it's research.

WILSON MIZNER
Perspectives in Biology and Medicine 1985

Differential Effects of 18- and 24-Gy Cranial Irradiation on Growth Rate and Growth Hormone Release in Children With Prolonged Survival After Acute Lymphocytic Leukemia

Alessandro Cicognani, MD; Emanuele Cacciari, MD; Vico Vecchi, MD; Marco Cau, MD; Antonio Balsamo, MD; Piero Pirazzoli, MD; Maria Teresa Tosi, MD; Pasquale Rosito, MD; Guido Paolucci, MD

 To evaluate the effects of two different doses of cranial irradiation on growth and growth hormone (GH) release, we studied 61 children with acute lymphocytic leukemia who had survived at least five years in continuous complete remission. Forty-three children received 24 Gy (group 1) and 18 children received 18 Gy (group 2). Height was evaluated at diagnosis, at the end of treatment, and 6, 12, and 24 months later. Growth hormone release was evaluated by arginine and levodopa tests after the end of treatment. After diagnosis, the height SD score decreased significantly in both groups; two years after the end of treatment, only group 1 showed an SD score for height that was still significantly lower than at diagnosis. Group 1 showed impaired GH responses to the tests and, compared with controls, group 1 in fact included a percentage of subjects with a normal response to levodopa (ie, >8 μ g/L) that was significantly lower (56.4% vs 83.3%) and a percentage of nonresponders to both tests that was significantly higher (21.6% vs 0%). These data indicate that only patients treated with lower cranial irradiation dosage (18 Gy) had complete growth recovery and normal GH responses to pharmacologic tests.

(AJDC 1988;142:1199-1202)

In recent years there has been a progressive increase in the number of children with prolonged survival after acute lymphoblastic leukemia (ALL). At present, long-term survival is reported in over 50% of patients treated. The introduction of central

nervous system prophylactic cranial irradiation has been one reason for this improvement in prognosis. Recent studies, however, have demonstrated that the delay of growth and impairment of growth hormone (GH) release reported in children not receiving therapy for ALL were primarily due to damage induced by radiotherapy.1-7 Radiotherapists have attempted to determine the smallest dose of radiation that can prevent the development of central nervous system leukemia and, at the same time, minimize radiation's negative effect on growth. A dose of cranial irradiation of only 18 Gy has been proposed and recent reports5.7 have suggested that 18 Gy is as effective as 24 Gy. The late effects on growth of this new approach, however, have been evaluated with too few subjects and for too short a time4,7 to allow any definitive conclusions.

To understand more about this problem we studied the growth and GH release of children who had not received therapy for ALL for at least two years and to whom we administered two different doses of prophylactic cranial irradiation, the first of 24 Gy and the second of 18 Gy.

PATIENTS AND METHODS

Sixty-one children (29 boys and 32 girls) in continuous, complete remission from ALL who had received no treatment for at least two years were examined. Since the duration of chemotherapy was three years, remission lasted five years in all cases. The mean (\pm SD) age at diagnosis was 4.90 \pm 2.47 years (range, 1.07 to 10 years) (Table 1). All patients were treated with chemotherapy according to the protocols of the Italian Society for Pediatric Haematology and Oncology (Table 2). They all re-

ceived cranial irradiation and were divided into two groups, according to the dose.

Patient Groups

Group 1.—A total of 24 Gy was administered over $2\frac{1}{2}$ weeks (12 fractions of 2 Gy each). This group included 43 subjects whose mean age was 5.27 ± 2.43 years (range, 1.07 to 10 years); 20 were male (mean age, 4.88 ± 2.33 years; range, 2 to 9.40 years) and 23 were female (mean age, 5.58 ± 2.51 years; range, 1.07 to 10) (Table 1).

Group 2.—A total of 18 Gy was administered over $2\frac{1}{2}$ weeks (ten fractions of 1.8 Gy each). This group included 18 subjects whose mean age was 4 ± 2.42 years (range, 1.07 to 9.5 years); nine were male (mean age, 4.10 ± 2.81 years; range, 1.3 to 9.5 years) and nine were female (mean age, 3.92 ± 2.18 years; range, 1.07 to 7.5 years) (Table 1).

The mean age of group 1 was not significantly different from that of group 2.

Growth Study

The standing height of each child was measured with a stadiometer. Most measurements were taken by the same person. Height was checked at diagnosis (before beginning treatment), at the end of treatment (three years after the beginning of treatment), and 6, 12, and 24 months after the end of treatment. The measurements were compared with normal values for age and sex with the tables of Tanner et als taken as the reference standard. To standardize the results and enable comparison with children of varying age and sex, we calculated the height SD score (SDS) from the formula $X - \overline{X}/SD$ (X indicates the measurement and X indicates the mean of the normal population). In girls with a bone age of more than 9 years and in boys with a bone age of more than 11 years the SDS was calculated using the mean value referring to bone age and the longitudinal standards of Tanner et al.8

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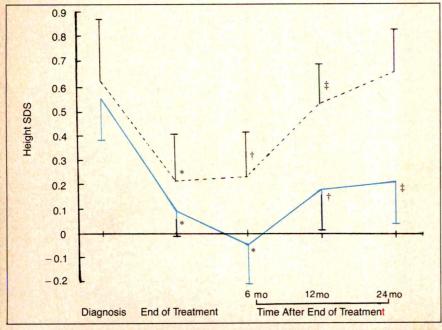
University of Bologna, Italy.

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| Table 1 | Table 1.—Mean Chronological Age of Study Population at Diagnosis | | | | | |
|-----------------|--|------------------------|-----------------------|--|--|--|
| | Group | | | | | |
| | 1 (24 Gy) | 2 (18 Gy) | Total | | | |
| No. of patients | 43 | 18 | 61 | | | |
| Age, y (range)* | 5.27 ± 2.43 (1.07-10) | 4.00 ± 2.42 (1.07-9.5) | 4.90 ± 2.47 (1.07-10) | | | |
| No. male | 20 | 9 | 29 | | | |
| Age, y (range)* | 4.88 ± 2.33 (2.0-9.4) | 4.10 ± 2.81 (1.3-9.5) | 4.64 ± 2.46 (1.3-9.5) | | | |
| No. female | 23 | 9 | 32 | | | |
| Age, y (range)* | 5.58 ± 2.51 (1.07-10) | 3.92 ± 2.18 (1.07-7.5) | 5.11 ± 2.51 (1.07-10) | | | |

^{*}Mean ± SD.

| No. of I | Patients | Chemotherapy | | | | |
|--------------------|--------------------|---|---|--|--|--|
| Group 1 (24 Gy) | Group 2 (18 Gy) | Induction | Consolidation | Maintenance | | |
| 25 | 5 | Prednisone, asparaginase, vincristine, daunorubicin hydrochloride | Mercaptopurine, methotrexate, prednisone | Mercaptopurine, methotrexate | | |
| 0 | 9 | Vincristine, prednisone | Asparaginase, cytarabine, thioguanine, doxorubicin | Mercaptopurine vincristine, methotrexate, prednisone | | |
| 6 | 2 | Doxorubicin, vincristine, methotrexate, prednisone | Asparaginase, cytarabine | Cytarabine, vincristine, methotrexate, prednisone, doxorubicin | | |
| 12 | 2 | Methotrexate, vincristine, prednisone | Asparaginase | Mercaptopurine, methotrexate | | |



Standard deviation scores (SDS) for heights (mean ± SEM) of patients grouped according to cranial irradiation dose. Significance compared with values at diagnosis is shown. Solid line indicates group 1 (24 Gy); broken line, group 2 (18 Gy); asterisk, P<.005; dagger, P<.001; and double dagger, P<.025.

Greulich and Pyle's atlas was used to evaluate bone age. Three children with more than one height measurement missing were excluded from the growth study.

GH Release Evaluation

Growth hormone secretion was evaluated in 58 subjects by means of an arginine and/ or levodopa test carried out on different mornings after overnight fasting. ¹⁰ Arginine hydrochloride (500 mg/kg; 10 g/dL, buffered to pH 7.4) was infused intravenously over 30 minutes and blood for the GH assay was collected at 0, 30, 60, 90, and 120 minutes. Levodopa was administered orally (290 mg/m²) and blood was collected at 0, 30, 60, and 90 minutes. ¹⁰

Informed consent was obtained from the patients' parents. Fifty-five patients underwent the arginine test (38 from group 1 and 17 from group 2), 54 underwent the levodopa test (39 from group 1 and 15 from group 2), and 51 patients underwent both tests (37 from group 1 and 14 from group 2). The tests were performed in all patients after treatment had been suspended for a mean $(\pm SD)$ period of 2.21 ± 0.9 years $(2.35 \pm 0.8 \text{ years in group 1 and } 1.75 \pm 1.1$ years in group 2). The mean times of testing for groups 1 and 2 were not statistically different. The results were compared with those obtained in 18 "short normal" control children (ie, healthy children with height <10th percentile and a GH response >8 µg/L in at least one pharmacologic test). The GH level was evaluated by specific radioimmunoassay (RIA Kit, Sclavo Siena, Italy).

Statistical Methods

For statistical analysis of the data analysis of variance was used for a simultaneous evaluation of the effects of treatment, age at diagnosis, and sex on the SDS for height. Changes in the SDS with time from diagnosis were assessed in the two groups on a within-subject basis by paired t tests and an analysis of variance model. The various parameters were compared using χ^2 analysis and Student's t test. Pearson's t correlation coefficient was also calculated.

RESULTS Anthropometric Data

The influence of treatment on growth rate was more evident in group 1. As shown by analysis of variance, only group 1 had significant differences between the SDS and control values (F=2.5; P=.044). The Figure shows the mean SDS in the two groups of patients. Two years after suspension of treatment, only group 2 had an SDS similar to the initial value, thus

showing complete recovery of height.

Analysis of variance showed the absence of a significant influence of age at diagnosis and sex on the final height. In group 1, however, 33.3% of male vs 66.6% of female subjects had decreases in height SDS greater than 0.5 SD (P<.025), and 30.7% of male vs 69.2% of female subjects had decreases greater than 1.0 SD (P<.05). Group 2 did not show differences between the two sexes (Table 3).

GH Values

Growth hormone values measured by pharmacologic tests were lower in patients than in controls, but the differences were not significant (Table 4). A GH peak of greater than 8 μg/L in at least one test was considered normal, whereas any response less than 4 μg/L was considered insufficient. Normal GH responses significient.

Table 3.—Patients With a Maximum Decrease of Height SD Score (SDS) Greater Than 0.5 and 1 SD

| SDS | No. (%) of Patients | | | | |
|---------------------------|------------------------|--------------|------|---------------|--|
| Maximum Decrease | | oup 1 Gy) | | oup 2 (Gy) | |
| >0.5 SD Total group | 27/41 | (65.8) | 9/17 | (52.9) | |
| Male subjects | 9 | (33.3)* | 4 | (44.4) | |
| Female subjects | 18 | (66.6) | 5 | (55.5) | |
| >1 SD Total group | 13/41 | (31.7) | 4/17 | (23.5) | |
| Male subjects | 4 | (30.7)† | 2 | (50.0) | |
| Female subjects | 9 | (69.2) | 2 | (50.0) | |

*P<.025 for difference with female subjects.
†P<.05 for difference with female subjects.

cantly different from those of controls were present only in group 1. These patients had significantly lower percentages of normal responses to the levodopa test (56.4% vs 83.3%; P < .05) and significantly higher percentages of absent responses to either test (21.6% vs 0%; P < .05) (Table 5). No correlation was found between SDS (expressed as an increase or decrease) and GH response to the tests in the entire group, among responders and nonresponders to both tests or to only one test, or among male and female subjects considered separately.

COMMENT

In recent years several reports have documented the long-term effects of treatment for ALL¹-7,12-21 on growth. Comparisons of the results of chemotherapy alone or in combination with cranial irradiation have shown that irradiation is the main cause of a slowing of linear growth velocity.¹-4,6,7 The existence of a relationship between the dose of radiation and impaired growth rate has led to trials of low dosages and, in recent years, a protocol of only 18 Gy was suggested. While results achieved thus far with the

18-Gy dose do not appear to show real advantages over results obtained with larger doses of radiation,4.7 our data indicate improved catch-up of growth in patients treated with 18 Gy. Only patients treated with 24 Gy showed a mean SDS for height still significantly lower than the measure obtained at diagnosis two years after the end of treatment. Since it is unlikely that a catch-up in growth would happen after this time, it seems probable that only the patients treated with 24 Gy did not completely recover their previous growth potential. Results differing from ours have been described by Wells et al4 and by Starceski et al,7 who reported that doses of 18 Gy and 24 Gy have similar influences on growth. However, only seven patients were treated with 18 Gy by Wells et al4 and the follow-up of these patients was too short (the first six months of treatment); Wells and colleagues4 themselves have suggested a longer control period before drawing any definite conclusion. Starceski et al7 compared growth rates in 18 children treated with 24 Gy and 19 children treated with 18 Gy. In their study the follow-up was only three years. All of

| Table 5.—Subjects With Normal (>8 μg/L) or Absent (<4 μg/L) Test Response | , |
|---|---|
| | _ |

| The same of the sa | No. (%) of Patients* | | | | | | |
|--|----------------------------------|-------------------------------------|-------------------------------------|--------------------------------|--|--|--|
| Group | GH Peak >8 μg/L in Both Tests | GH Peak >8 μg/L in Arginine Test | GH Peak >8 μg/L in Levodopa Test | Nonresponders to Both Tests | | | |
| Total | 24/51 (47) | 34/55 (61.8) | 34/54 (62.9) | 10/51 (19.6)† | | | |
| Group 1 (24 Gy) | 17/37 (45.9) | 25/38 (65.7) | 22/39 (56.4)† | 8/37 (21.6)† | | | |
| Group 2 (18 Gy) | 7/14 (50.0) | 9.17 (52.9) | 12/15 (80.0) | 2/14 (14.2) | | | |
| Controls (n = 18) | 11 (61.1) | 14 (77.7) | 15 (83.3) | 0 (0) | | | |

*GH indicates growth hormone.

†P<.05 for difference with control subjects.

| Table 4.—Growth Hormone Values in Study Subjec | cts and 18 Short-Normal Control Subjects |
|--|--|
|--|--|

| | | Mean (±SD) Growth Hormone Level, μg/L | | | | | |
|-----------------|-------------------------------|---------------------------------------|--------------|---------------|----------------|--------------|---------------|
| | | | Levodopa | | | Arginine | |
| Group | No. of Patients | Basal Value | Peak | Area | Basal Value | Peak | Area |
| Control | 18 | 3.4 ± 4.53 | 14.04 ± 8.73 | 23.00 ± 13.74 | 2.99 ± 3.10 | 13.63 ± 8.36 | 26.1 ± 17.9 |
| Group 1 (24 Gy) | Levodopa, 39; arginine, 38 | 2.24 ± 1.97 | 10.13 ± 6.38 | 17.49 ± 11.5 | 2.67 ± 2.8 | 12.08 ± 6.64 | 28.0 ± 29.6 |
| Group 2 (18 Gy) | Levodopa, 15; arginine, 17 | 3.28 ± 2.98 | 11.08 ± 9.02 | 19.29 ± 13.67 | 1.98 ± 1.11 | 9.77 ± 6.23 | 19.61 ± 13.95 |

our patients went through a two-year control period after the end of treatment, with an overall follow-up of at least five years. In our two groups of patients, as in the patients of Starceski et al, we would have observed no significant differences in growth rate if we had considered only the situation three years after diagnosis, ie, at the end of treatment, when both groups showed a similar decrease in SDS compared with the initial value (P < .005).

Given the dose of radiation used, sex also showed a certain influence on growth. Among our patients, girls showed a higher sensitivity than boys to the inhibition of growth caused by radiation. However, this differing response between sexes was only evident in the group treated with the larger dose of radiation. Height loss in children with ALL who were not receiving therapy may indicate radiation-induced hypothalamic or pituitary damage that caused decreased GH secretion.14-21 While GH release abnormalities following cranial irradiation with 24 Gy are well documented,17,18 we are unaware of any data on subjects treated with 18 Gy.

Our results indicate that GH secretion in children treated with 18 Gy is less compromised. Only in the 24-Gy group did we observe a higher than normal percentage of insufficient responses to both tests (P < .05), and the percentage of normal responses to the levodopa test was lower (P < .05) compared with controls. It must be emphasized, however, that 14% of patients treated with 18 Gy have already demonstrated GH deficiency by provocative testing, and therefore there still may be substantial endocrine consequences even after treatment with only 18 Gy. The mechanism by which arginine induces a GH secretion is not yet entirely established. Some investigators have postulated that it may act directly on the pituitary gland,22 while levodopa acts through a dopaminergic neuronal pathway leading to the stimulation of the hypothalamic GH-releasing hormone.23 Treatment with 24 Gy seems primarily to affect GH secretion induced by levodopa, indicating selective damage to the hypothalamic GH-releasing center. This probably is not likely to occur with the lower radiation dose, suggesting lighter or merely transitory damage to the hypothalamus.

Like others, 14-18 we found no correlation between GH response to tests and growth rate. Somatomedin C assays and recording of spontaneous GH release during the day or at night24 perhaps would have allowed better understanding of this finding. As reported in patients operated on for craniopharyngioma,25 the presence of normal somatomedin C values might explain a good growth rate independent of the GH response to stimulation tests. On the other hand, it has been found that children who have received cranial irradiation may show a decrease in spontaneous GH release, despite the disclosure of releasable pituitary stores of GH by arginine and levodopa stimulation tests. 17,18 Hence, although these tests can demonstrate the impairment of pituitary function in at least some of these patients, they cannot identify all the subjects with a defect of GH release.

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Hysterical Conversion Reactions Mimicking Neurological Disease

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 Seven children with illnesses diagnosed as hysterical conversion reactions (HCRs) were treated at our institution over a period of nine months. They all had neurological symptoms that included one or more of the following: paralysis, headache, seizures, and episodic blindness. All patients but one were misdiagnosed as having an organic disease prior to our final diagnosis. Five children were treated with medications for presumed organic ilinesses. In all of these children a diagnosis of HCR was made on the basis of their history and neurological examination findings. They all recovered or began recovery within a few days of having HCR diagnosed, and none of them had had a relapse three to 11 months after the diagnosis of HCR was made. We believe, and there is ample evidence in the literature, that a positive diagnosis of HCR in childhood can be made when neurological manifestations cannot be explained on an anatomic and physiological basis. Although absence of an obvious organic cause is a helpful clue, exhaustive exclusion of all possible organic causes is not necessary for the diagnosis of HCR.

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Hysterical conversion reactions (HCRs) in children can be diagnosed accurately. However, the diagnosis is often overlooked, or it is considered and discarded. Neurological symptoms are often the major manifestation of HCRs. More often than not, such children are subjected to a diversity of investigations because of concern about missing an organic lesion, pressure from parents, criticism from colleagues, and fear of medical litigations. Most physicians consider HCR a diagnosis of exclusion. A review of the literature suggests, and we agree, that a positive diagnosis of HCR can be made on the basis of

history and physical examination findings in most cases. Parental acceptance of the diagnosis is also often dependent on the speed and certainty with which it is made. The purpose of this report is to describe seven patients, aged 9 to 15 years, diagnosed as having HCR on the basis of symptoms and signs inconsistent with known patterns of anatomy and physiology.

PATIENTS

Six children were referred to our institution for further evaluation of their neurological symptoms. These six children constituted 1.7% of inpatients evaluated for neurological problems during a ninemonth period. The seventh patient, an outpatient, had previously been followed up by the pediatric neurology service because of dominantly inherited dystonia. Ages ranged from 9 to 15 years (mean, 12.3 years; median, 12 years).

All six inpatients had an incorrect diagnosis made at the time of referral to the pediatric neurology service. The seventh patient had a correct diagnosis made in the emergency department. Six of the seven children had received unnecessary laboratory investigations or treatment prior to the correct diagnosis. The neurological examination, correlated by the history, was diagnostic of HCR in all patients. There was no recurrence of the primary conversion symptom four to 33 months after diagnosis (mean, 16.6 months; median, 20 months). Neurological manifestations, diagnoses considered, investigations performed, and treatment given before a diagnosis of HCR was made are given in Table 1. Treatment, condition at discharge, follow-up after discharge, and nature of follow-up are given in Table 2. Similar to Maisami and Freeman,1 we used a team approach to evaluation and treatment in which psychiatric intervention and ancillary support services were enlisted as soon as the diagnosis of HCR was considered (Table 2).

COMMENT

Hysterical conversion reaction is thought to represent the somatic manifestations of an unbearable emo-

tional conflict and is also a powerful tool that helps the parents and patients to deal with the conflict.2 It is distinguished from malingering, which is an intentional attempt to deceive. There is no consensus about the incidence or prevalence of HCR. 8.4 The reported occurrence varies from 2% of pediatric neurology inpatients during 41/2 years to 13% of child psychiatry cases. In most cases, HCR presents as neurological dysfunction,5 and it can manifest any neurological symptom or sign.5-18

Onset of neurological symptoms in a previously healthy child is alarming to the family and physician alike. The physician may be reluctant to consider HCR without further investigations.14 The biopsychosocial profile of the family may give important clues to the underlying cause of the symptoms. Maloney,15 in a retrospective study of 105 inpatient children with a diagnosis of HCR compared with a similar number of controls, found a high frequency of recent family crisis (97%), unresolved grief reactions (58%), and family communication problems (77%). In the children with HCR studied by Rock,³ there were often poor peer relationships (not recognized by the parents), elements of depression, overdependency, a lack of concern for symptoms, parents with interpersonal problems, and a parent who promoted the conversion symptom or the dependency. The physician may not make appropriate inquiry, and some children or family members may conceal important information. This is illustrated by our patient 1. It was not until HCR was diagnosed, on the basis of her neurological examination, that she disclosed the suicide of her best friend and the threatened suicide of several other friends-events that preceded her HCR by a few weeks. While the psychosocial history, the absence of a predisposing illness, and a negative family history of a neurological illness may help one to consider HCR in the

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differential diagnosis, it is the observation of the child and the neurological examination findings that are critical in making such a diagnosis.

We discuss below the most common types of HCR that mimic neurological disease.

Seizures

Seizures are the most common manifestation of HCR.⁵ Before referral to us, patient 5 was given a loading dose of phenobarbital sodium for suspected seizures. However, aspects of the generalized episodes that were inconsistent with generalized convulsive epileptic seizures included maintenance of full consciousness, responsiveness

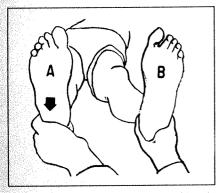


Fig 1.—Patient in recumbent position is asked to press down on examiner's hands placed under heels (arrow indicates direction). Pressure is felt only from nonparalyzed leg in both organic paralysis and pseudoparalysis. A indicates nonparalyzed leg; B, paralyzed leg (organic paralysis or pseudoparalysis).

to verbal commands, and the ability to stop her abnormal movement when asked. Moreover, her jerking movements occurred only in the presence of her parents. In addition, she lacked features that, although nondiagnostic, lead one to suspect an epileptic seizure, ie, incontinence of urine, bitten tongue, and postictal confusion or sleepiness.

Patient 6, who had episodic blindness and paroxysmal electroencephalographic (EEG) abnormalities, had no response to carbamazepine therapy or its withdrawal and no electrographic correlate on video-EEG monitoring. The mirror test⁸ conclusively excluded blindness during an episode of purported blindness (see "Visual Dysfunction" section). Pseudoseizures may occur in patients who also have epileptic seizures. Holmes et al,16 using video-EEG monitoring, documented pseudoseizures in 11 of 53 pediatric patients with intractable seizures. Eight of the 11 patients with pseudoseizures, however, also had epileptic seizures. In these patients, epileptic seizures were often characterized by postictal confusion or drowsiness, urinary incontinence, and a change in frequency of spells with a change in antiseizure medications. By contrast, in pseudoseizures, a postictal state was less common and often absent, incontinence of urine did not occur, patients were often combative or used vulgar language, antiseizure medications did not change seizure frequency, and there was a frequent relationship to stress.

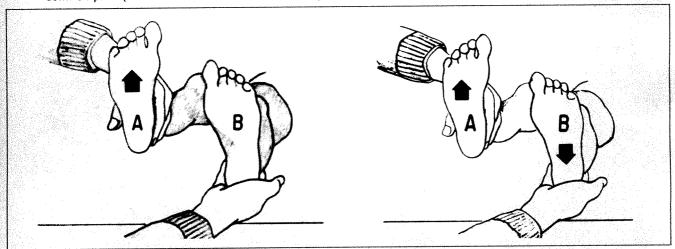
Serum prolactin level may be elevated 20 minutes after generalized tonic-clonic and complex partial seizures, and serum creatine kinase level may be elevated 24 to 48 hours following generalized tonic-clonic seizures, but neither is elevated following pseudoseizures. ^{17,18} A normal value of either should be interpreted cautiously because it neither excludes an epileptic seizure nor is diagnostic of a pseudoseizure.

Paralysis

Paralysis affecting one or more limbs is the second most common presenting feature of HCR.⁵ Muscle tone may be decreased in HCR, and there may even be disuse atrophy (patient 2) or contractures when paralysis is longstanding.^{12,19} For reasons unknown, conversion hemiparesis almost always affects the left side.¹⁰

The most important differentiating points between true paralysis and pseudoparalysis are presence of normal and symmetric deep-tendon reflexes and bilateral downgoing plantar responses with pseudoparalysis. 6,10,12 If any asymmetry or equivocal signs are present on serial examinations, and the differential diagnosis includes a potentially irreversible problem, eg, spinal cord compression, expeditious investigation to exclude an organic lesion may be necessary. Similar to pseudoparalysis, deep-tendon re-

Fig 2.—Patient is asked to raise nonparalyzed leg against examiner's hand on ankle. Left, In true hemiplegia, insignificant added pressure will be felt by hand that remained beneath heel of paralyzed leg (arrow indicates direction of movement). A indicates nonparalyzed leg; B, paralyzed leg. Right, In pseudoparalysis, heel of supposedly paralyzed leg will press down on palm (arrows indicate direction of movement). A indicates nonparalyzed leg; B, supposedly paralyzed leg.



| Patient No. | | | Investigations | Treatment Prior to Discharge | | |
|--|-------------------------------------|--|--|---|--------------------------------------|--|
| 1 15/F Paroxysmal severe headache, left hemiparesis, left hemianesthesia | headache, left hemiparesis, left | Postconcussive headache, pheochromocytoma | Numerous blood tests, CSF profile, CT/MRI brain scans, abdominal CT scan, renal isotope scan, urine assay for VMA level, EEG, EKG | Hydroxyzine hydrochloride clonidine hydrochloride, nifedipine, phenytoin sodium, propranolol hydrochloride, secobarbital sodium | | |
| 2 | 12/ M | Quadriparesis, hypophonia, generalized muscle atrophy and hypotonia | Meningoencephalitis, AIDS, Reye's syndrome, seizure disorder, Guillain Barré syndrome | Numerous blood tests, CSF profile, EEG, EMG/NCV studies, brain CT scan | Antidepressants, IV vitamin infusion | |
| 3 | 12/F | Acute paraplegia with normal bowel and bladder function | Paraplegia of unknown origin | Myelogram with follow-up CT scan | None | |
| 4 (4.8%) | 11/M | Paraplegia with normal bowel and bladder function | Arthritis | None | Anti-inflammatory drugs, crutches | |
| 5 5 | 9/F | Multifocal and generalized jerking of extremities without loss of consciousness | Seizure disorder | EEG | Phenobarbital sodium | |
| 6 | 14/M | Recurrent transient total visual loss almost daily | Seizure disorder; migraine | EEG, brain CT scan | Carbamazepine | |
| 7 | 13/M | Right-eye blindness | Hysterical monocular blindness, labyrinthitis (severe vertigo and headache occurred concurrently with blindness) | Canal paresis on ice water energy testing | None | |

*CSF indicates cerebrospinal fluid; CT, computed tomographic; MRI, magnetic resonance imaging; VMA, vanillylmandelic acid; EEG, electroencephalogram; EKG, electrocardiogram; AIDS, acquired immunodeficiency syndrome; NCV, nerve conduction velocity; and IV, intravenous.

flexes may be normal in diseases such as myasthenia gravis, thyroid myopathy, and polymyositis. An acute spinal cord lesion is characterized by paresis or paralysis of extremities in the presence of normal mental status and cranial nerve function, but in contrast to the normal reflexes in our patients 2. 3, and 4, such a lesion is associated with absence of deep-tendon and cutaneous reflexes and later evolves to hyperreflexia and extensor plantar responses. Neurogenic bowel and bladder are common. The presence of normal deep-tendon reflexes rules out Guillain-Barré syndrome.

Several maneuvers can be used to further corroborate the hysterical nature of the patient's symptoms. A commonly used method is the Hoover's sign (Figs 1 and 2) in which the supposedly paralyzed leg presses forcefully on the examiner's palm (patient 1). Observing the child move supposedly paralyzed limbs during sleep (patient 2) not only confirms the diagnosis of HCR but, more importantly, convinces family members of the correctness of the diagnosis. Another maneu-

ver is to hold a patient's flaccid, paralyzed arm directly over the face and then drop it. In pseudoparalysis, the arm does not fall into the patient's face but instead falls to one side.

Sensory Symptoms

Apparent sensory symptoms in a patient with HCR may take several forms. Pain is more common than sensory loss. Sensory impairment due to organic disease may follow a dermatomal pattern, and there is usually a border zone of sensory impairment between clearly abnormal and normal areas. In contrast, in HCR, sensory symptoms are frequently sharply limited and do not follow a known anatomic or dermatomal pattern.

Patients with HCR do not feel a vibrating tuning fork that is placed in the area of sensory loss on the forehead (patient 1), whereas patients with organic disease will perceive vibration when the tuning fork is placed over the anesthetic skin because vibrations are transmitted by bone underneath the anesthetic skin to the area with normal sensations.

Visual Dysfunction

Patients with hysterical visual loss never hurt themselves in spite of marked impairment of vision (patient 6). The presence of opticokinetic nystagmus (OKN) can document that vision is present provided the patient fixates on the alternating stripes of OKN tape or drum. Absence of OKN can be due to lack of fixation as well as blindness. A more useful test involves holding a mirror in front of the patient's open eyes and tilting it back and forth and then up and down. A seeing patient will move his eves irresistibly during an episode of blindness (patient 6).

Patients with hysterical visual field defects report the physiologically impossible state of a constant field size regardless of their distance from the test object. Normally, the visual fields enlarge proportionately to the distance from the test object.⁸

Double vision on a hysterical basis is easily distinguished from imbalance of eye movements by covering one of the patient's eyes. If diplopia persists with an eye covered, ie, monocular

| Patient No. Treatment | | Condition at Treatment Discharge | | Nature of Follow-up | |
|--|---|---|--|--|--|
| Inpatient psychiatry, physical therapy, outpatient psychotherapy declined by parents | No headaches or hemiparesis | At 4 mo no medications, asymptomatic | Telephone with parents | | |
| 2 | Inpatient psychotherapy for 2 wk (discharged against medical advice), social work counseling, physical therapy | Walking without support, normal voice | At 4 mo no medications, some difficulty in climbing stairs but steady improvement | Telephone with parents | |
| 3 | Inpatient psychotherapy for 2 mo, physical therapy, social work counseling, outpatient psychotherapy for 27 mo | Walking independently | At 33 mo no leg symptoms, new onset of pseudoseizures that resolved with family therapy | Telephone with treating psychiatrist | |
| | Inpatient psychotherapy for 1 wk, physical therapy, social work counseling, outpatient psychotherapy for 18 mo | Walking without assistance | Normal at 6 mo, at 28 mo runs slowly | Examination by author at 6 mo, telephone with guardian (grandmother) at 28 mo | |
| 5 | Inpatient psychotherapy for 1 wk, social work counseling, outpatient mental health center for 2 visits and then failed to return | Asymptomatic | At 4 mo no medications, asymptomatic | Telephone with parent | |
| 6 | None (psychiatric treatment recommended) | Symptoms continued at discharge | At 20 mo no medications, asymptomatic | Telephone with private physician | |
| 7 | None (psychiatric treatment strongly recommended) | Not hospitalized | At 1 mo no complaints, at 19 mo episodes of headache without other complaints | At 1 mo clinic visit with authors, at 23 mo telephone with family physician | |

diplopia, it is likely to be an HCR. Rare organic causes of monocular diplopia include retinal detachment or abnormalities of the vitreous or lens. If horizontal diplopia consistently disappears when either eye is covered, it is likely due to third or sixth cranial nerve dysfunction.

True monocular blindness can also be detected by asking the patient to read a page of material with small print while a pencil is held vertically between the patient and the page of material. The person who is truly blind in one eye will be unable to read some

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words, but stereoscopic vision that is present in a patient with hysterical monocular blindness allows the subject to "see around" the pencil and continue to read.

Just as HCR can mimic neurological diseases, the behavioral aspects of neurological diseases may falsely suggest psychiatric diseases. Rivinus et al²⁰ described 12 patients who developed infectious, neoplastic, or degenerative neurological diseases two to 71 months after their original psychiatric diagnoses were made. Harcourt and Hopkins²¹ reported four

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cases of tapetoretinal degeneration that started as behavioral disturbances. Similarly, we have seen several cases of neuronal ceroid lipofuscinosis in which the initial behavioral abnormalities obscured the slowly progressive cognitive dysfunction. To avoid diagnostic errors, Tissenbaum et al²² stressed the importance of multiple examinations, adequate follow-up, and training in neurology.²¹

The illustrations were drawn by Joan M. Hellquist. The authors wish to acknowledge the secretarial assistance of Beth Oliver and Becky Gunter.

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Pediatric Perspectives



The Future of Subspecialty Training in Pediatrics

Michael S. Kappy, MD, PhD

The conference entitled "The Future of Subspecialty Training in Pediatrics" was the second annual conference on issues in pediatric education held under the auspices of the Children's Health Center of St Joseph's Hospital, Phoenix. The conference was conducted from Oct 9 through 11, 1987, in Scottsdale, Ariz, and was cosponsored by the Flinn Foundation, Phoenix; Ross Laboratories, Columbus, Ohio; and Mead Johnson & Co. Evansville, Ind. The following were the main speakers: William Cleveland, MD, professor and chairman, Department of Pediatrics, University of Miami School of Medicine; Vincent Fulginiti, MD, Vice Dean for Academic Affairs, University of Arizona, College of Medicine, Tucson, and Editor, AMERICAN JOURNAL OF DISEASES OF CHILDREN; Birt Harvey, MD, Chairman, District 9, Executive Board, American Academy of Pediatrics, Palo Alto, Calif; and Thomas K. Oliver, Jr. MD, Senior Vice President, American Board of Pediatrics, Chapel Hill, NC. Participants included pediatric department chairmen and fellowship program directors from ten programs primarily in the western and midwestern United States and pediatricians from Phoenix and Tucson. The conference participants addressed the following five topics: the role of subspecialists in general pediatric training, the division of labor for subspecialists, the role of community subspecialists in training programs, funding sources for subspecialty training, and the need for uniform standards in subspecialty fellowship training.

THE ROLE OF SUBSPECIALISTS IN GENERAL PEDIATRIC TRAINING

The consensus of the participants was that subspecialists are and should remain general pediatricians and that they should participate significantly in general and subspecialty pediatric teaching rotations. Because of the complexity of the relationship of subspecialists to general training programs, a coordinator of residency curriculum should help subspecialists integrate their contribution to the residency program. The major obligations for subspecialists in pediatric residencies, therefore, are the following: (1) Define the "minimal functional competency" in their field for the graduating resident. (2) Negotiate with residency curriculum coordinators to develop realistic subspecialty content for pediatric residents. This includes the percentage of individual subspecialty curricular time in the residency and in the specific subspecialty content. (3) Assist individual residents to increase their knowledge in a weak area and to pursue areas of interest and strength, possibly with different curricula.

The primary determinant of "functional competency" will be the extent to which practicing pediatricians deal with subspecialty problems. Because general pediatricians may provide most (up to 80%) subspecialty care in the future, subspecialists will be more academic center-based to provide secondary and tertiary care, do complex procedures, teach, and generate new knowledge in their field.

Deemphasizing the pediatric subspecialist in private practice would emphasize the consultative abilities and functions of the general pediatrician. In contrast, internal medicine programs certify more cardiologists in less than a decade (6000) than all of

the subspecialty fellows in pediatrics. Furthermore, subspecialty training in internal medicine is producing clinical competitors who tend to practice in the community.

Some participants thought that the generalist, not the subspecialist. should be the primary teacher on the wards and in the clinic; subspecialists should not be role models for residents going into general pediatric practice because they tend to overrefer to other subspecialists. They also may fail to teach total patient care on the wards or in the clinics. Instead, the subspecialist has the obligation to teach the resident the "subtleties" of the field (ie, the less common presentations, the unexpected complications, the less frequently used therapeutic modalities, and the pathophysiology of specific subspecialty conditions). As Joe St Geme, MD, was quoted by one participant, "The generalists practice subspecialty medicine for which they have been prepared, examined and certified and which they can do more efficiently, more gracefully and less expensively than a subspecialist or a fleet of subspecialists."

A major problem about the role of generalists on pediatric faculties was raised. Specifically, generalists on faculties cannot support themselves since they do not do complex (remunerative) procedures, do not garner research support, and cannot generate enough income from the primary care they provide in an academic setting. Therefore, a pediatric department could not afford enough generalists to provide the suggested role models. Furthermore, conflict with pediatricians practicing in the community could develop unless the hospital-based role of the generalist was clearly circumscribed.

Alternatively, many of the participants supported teaching models where generalists and subspecialists

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provide dual attending functions. Regardless of this possibility, a need was expressed for increased involvement of general pediatricians in the community to provide subspecialty teaching because many larger academic centers cannot provide a suitable mix of secondary and tertiary care patients. Residents training in the community, however, would be exposed to the "real world" and to the experience of coordinating holistic care for patients. This exposure would also impress the importance of cost-effectiveness in patient management on the resident.

The role of the "hobbyist," a general pediatrician with perhaps a year's fellowship in a subspecialty who might consult within a large group, was discussed, and several disadvantages were apparent. First, it would discourage others in the group from participating in certain subspecialty fields. Second, referrals from outside the group would not occur because the hobbyist would still be in private pediatric practice. Third, hobbyists would gradually lose subspecialty competence if they did not remain sufficiently immersed in the subspecialty and did not maintain subspecialty collegial relationships.

Finally, better communication among subspecialists and generalists was urged because the subspecialist has an ongoing responsibility to work with the referring physician in managing a given patient's condition. In the ideal relationship, the subspecialist does not assume the management of the child; rather, a partnership is developed. Teaching this skill should be a major goal of both generalists and subspecialists on pediatric faculties.

DIVISION OF LABOR FOR SUBSPECIALISTS

A possible division of labor would be patient care (20% to 30% of the subspecialist's time), teaching (10%), and laboratory-based research (60% to 70%). The time allotted to research recognizes the increased demand for research-oriented fellowship programs and the increasing role for the subspecialist as researcher. The rapidly changing influence of finances in determining professional roles is not accounted for.

Twenty years ago faculty subspecialists had little or no private practice. They saw patients (largely indigent) who came to university centers for care, and they were not expected to bill patients for their services. The existing financial situation has drastically modified the roles of faculty in subspecialty divisions. Salaries now depend on identifying the amount that the state, the university, or both contribute to the subspecialist's support. The remainder is the salary gap that the faculty member must earn through grant support or patient care. Members of the faculty are also responsible for earning their fringe benefits; only thereafter can incentive programs be developed. Incentive programs are highly variable and may be based on productivity, but defining productivity is also difficult. Thus, faculty members experience considerably increased responsibilities to treat patients. In addition, subspecialists must undergo an academic review process that allots six years to achieve promotion and tenure, and they are expected to perform "significant" research that will meet the criteria of their peers. This process, of course, is also highly variable, cannot be defined a priori, and is retrospectively judged. While individuals are not expected to serve on committees during their first year, they are expected to participate on many thereafter. Faculty members are also expected to contribute to the fiscal planning of the department, to quality assurance functions, to medical student clerkships, to house-staff recruitment, and to curriculum planning.

These heavy demands may be responsible for the departure of younger faculty members; not surprisingly, 40% choose not to practice in academic centers after their fellowships. Furthermore, subspecialists may leave academic centers and enter private practice after brief faculty careers. This trend may be related to the burden of providing increased patient care.

The difficulty associated with a subspecialist performing all of these roles well, earning a salary, and meeting the requirements for promotion and tenure led to the suggestion that departments be divided into two or more career tracks: one would empha-

size research (tenure track) and the other would emphasize clinical care. Both would include teaching responsibilities. The nontenure track would encourage recruitment of more clinician-teachers into subspecialty divisions; however, such individuals must retain their sense of academic inquiry (ie, the generation of new information). Individuals in research, conversely, must maintain their clinical skills. Thus, even a two-track system would overlap considerably. Ideally, however, subspecialists would do what they do best-the division among patient care, teaching, research, and administrative labors would depend on an individual's talents.

Several participants supported the idea that more than one track would have to be developed in pediatric departments to accomplish all of the department's goals; however, equal benefits for faculty members in both tracks would have to be developed. The concern was voiced that only the research-oriented individual would be rewarded with tenure and other privileges (eg. voting rights). Tenure is awarded more for basic than for clinical research, and the clinical track might be viewed as second class, even though clinician-teachers are critical to the survival of all departments and form a unifying basis for resident education. The participants agreed that a uniform definition of "scholarship" is difficult; however, both tracks would be composed of individuals who saw the creation of new information as a major goal. Subspecialists, whether clinical or basic, would have to devote significant time to investigation; otherwise, pediatric departments would have no raison d'être. Universities and other academic centers exist to discover new knowledge. This commitment cannot be reached with two totally separate (ie, research and nonresearch) tracks for faculty members.

Yet, in a single-track system such as exists in most departments, individuals must spend at least 40% of their time on research. Financial demands dictate that they spend 40% of their time caring for patients; only 20% or less of their time is available for teaching and all other responsibilities, including administrative. Clearly, the system is impractical in the future.

THE ROLE OF COMMUNITY SUBSPECIALISTS IN TRAINING PROGRAMS

Most participants favored incorporating community subspecialists into teaching programs. Ideally, there would be no competition, no problems with egos, and no territorial disputes with respect to who directed the educational process. Still, some community physicians do not view teaching as a goal and do not want students and residents treating their patients. Thus, a control issue subservient to the educational process develops. If serious enough, residents may be excluded or included inappropriately if they are merely asked to provide service. Generally, an academic institution suffers if it fails to take advantage of all the talent present in the community; relationships can usually be negotiated with each party compromising, if necessary, in exchange for a partnership.

In general, four groups benefit from this cooperative involvement. (1) For university or academic institutionbased faculty members, the relationship broadens their clinical perspective, gives a larger patient population for teaching and research, and provides additions to the faculty gratis. (2) For the community subspecialists, the relationship also broadens their perspective, gives peer-interaction stimuli, updates their knowledge, and provides additional motivation to keep current because of their teaching responsibilities. (3) The house staff sees a wider variety of patients; they are exposed to different methods of care and different role models; and they experience more real world management of subspecialty problems. (4) The patients receive increased benefit from the sum of the experience of the three physician groups.

The example of free-standing children's hospitals coexisting in a city with a university was cited as the purest example of the benefits of integrating community physicians with their university counterparts in resident education and patient care.

The point was reemphasized that primary care pediatricians should also be integrated into training programs, perhaps even before considering subspecialists. The changing financial situations in academic centers make new, cooperative relationships between community physicians and universities and other academic centers mandatory.

An institution will be diminished unless community and academic center-based subspecialists work together. If these relationships can be established, then each group can contribute to residency training programs and to the excellence of the institution. Furthermore, developing joint ventures with community physicians to support education and research was strongly supported, as was the possibility that revenue from private physicians could contribute to residency programs, fellowship training programs, or both.

FUNDING SOURCES FOR SUBSPECIALTY TRAINING

There was unanimous agreement that the answer to the question "who should pay?" is, "anyone who will." Generally, five sources of funding were identified. (1) Historically, hospitals have paid for research, especially in surgery programs (eg, neurosurgery). Furthermore, at least one year in pediatric fellowship is typically devoted to research, and hospitals have supported this as a contribution to their own research and development. Nevertheless, because of third-party payors' (including Medicare) increasing resistance to subsidizing medical education, hospital support may not be a viable option as the sole support of subspecialty training in the future. (2) Outside agencies may be able to contribute to fellowship training. For example, in pulmonology, the American Thoracic Society, Cystic Fibrosis Foundation, and local groups, including pharmaceutical companies, may be able to help support training. (3) Professional fee revenues generated by faculty, especially in cardiology, pulmonology, gastroenterology, and neonatology, could partially support fellowship salaries. This source of funding could include contributions from the private community, if private physicians would be willing to pool income to fund their eventual replacements. (4) Legislative contributions are another potential avenue of fund-

ing. The concept that "today's research is tomorrow's care" may be used to lobby for increased residency and subspecialty training funds from state legislatures (in state medical schools) or through Congress. In addition, loan-forgiveness programs to help fellows finish their training might encourage more individuals to pursue subspecialty careers, especially since many students are heavily in debt after medical school. (5) Fellows themselves, if fully licensed, could charge fees for certain services they provide while in training, thereby partially supporting their own training.

Multiple payors could also contribute to fellowship training, depending on how fellows spend their time. For example, research efforts by fellows could be paid by grants, teaching efforts by the universities (or hospitals). working with house staff by hospitals. and professional fees by seeing patients. Federal and state governments should also be obliged to support research and development aspects of fellowships because a resource for the nation's future is being created. State legislatures might be convinced to fund fellows at state universities because residents and fellows tend to practice in the state in which they were trained.

THE NEED FOR UNIFORM STANDARDS IN SUBSPECIALTY FELLOWSHIP TRAINING

Most participants agreed that although a two-track system may be necessary for subspecialists on faculties, all subspecialists should receive the same core training (viz, three years of general pediatrics to enable them to practice their subspecialty better and three years of fellowship training). Uniform training would ensure that the clinically oriented candidate had some investigative skills and would serve as an introduction for the research-oriented candidate.

Fellowships could provide a year of clinical work, a year of research, and a year of combined clinical and research experience in all subspecialty training programs even while recognizing that 1½ years of research training would be inadequate to train "tenure track" individuals fully to do research. Ultimately, individuals who

pursue careers as clinician-teachers may receive different training than individuals who pursue more basic research-oriented careers.

By definition, therefore, two kinds of research training could be incorporated into fellowship programs: basic laboratory research and clinically or epidemiologically oriented research. Different fellowship programs could incorporate one or the other aspect as their research component. This flexibility would recognize that not all institutions (particularly those that lack the capabilities to provide rigorous training in basic research) would be able to train all subspecialists. This was considered appropriate, since the future of subspecialty trainees is variable, as stated earlier. Some subspecialists, in fact, will never interact with an academic health center—a reality that must be acknowledged.

What emerges from fellowship training, therefore, is the recognition that research is a discipline, not a trade. The spirit of inquiry and the ability to analyze, to think clearly and objectively, and to express the results of investigative efforts must be taught in all programs.

The difficulty in certifying research competence as opposed to research time was discussed at length. Criteria such as "potential" or "promise" in faculty applicants were raised without much agreement on definition. Can a newly trained subspecialist be required to publish a report in a peer review journal or to prepare a successful RO-1 grant? Both criteria were considered impractical. It was suggested that the real certification in subspecialty medicine is to acquire a body of knowledge in a field. The ability to do research would be "tested" during the individual's career.

The participants agreed that all subspecialties should develop processes of American Board of Pediatrics certification, or chaos in subspecialties will develop. In the past, the quality and quantity of programs without boards have been more variable than those with boards. For example, some infectious disease fellowships are one year, some are two years; some are rigorous, some are sloppy. The lack of board structure and standards in these areas may lead to two standards

of subspecialty practice. The participants vigorously supported the idea that all acknowledged subspecialties should be accredited in the same manner.

CONCLUSIONS

The conference participants acknowledged that the nature of fellowship training and subspecialty practice in the future is being strongly influenced by several distinct but interrelated factors. Achieving financial solvency is a rapidly growing burden for the academic center-based subspecialist. Twenty years ago little, if any, of an individual's salary came from direct patient revenue; now, 50% (or more) of an individual's support may be sought from this source. Concomitantly, promotion-tenure processes place continued demands for the subspecialist to generate new basic knowledge through research. Besides, many prefer to do research rather than to treat and bill patients as a majority time commitment. Thus, the development of a two-track system that separates these functions (in part) is being considered at many institutions.

For the clinician-teacher, the added element of competition within the community must be considered, and departments of pediatrics will have to address their relationships with community subspecialists (and generalists) with care. In an ideal world, such "joint ventures" would provide new opportunities for resident education, patient care, and funding in subspecialty areas.

For the researcher, even the now proposed three-year fellowships may be inadequate preparation for a career in which competition for grant funding with more experienced PhDs may put the subspecialist at a disadvantage. Thus, even the most rigorous three-year training may have to be extended to provide a more intense experience in basic research.

Funding for current fellowships (not to mention extended research fellowships) is already considered a serious problem. Hospitals and third-party payors confront an increasing need to pare and contain escalating costs of medical care. Other sources of funding must be identified if fellowships are to survive in the 20th century, and addi-

tional demands for subspecialists to generate patient revenue to support fellowship programs will occur.

A redefinition of the role of the subspecialist is rapidly approaching. As general pediatricians seek more responsibility to provide a consultative role in the community and to provide "total" care for their patients, they will manage an increasing percentage of subspecialty problems in their practice without subspecialty consultation. Some conference participants expressed the opinion that it is both necessary and desirable for the general pediatrician to manage 75% to 80% of all subspecialty problems in the future. Clearly, this trend would impact both the economics of subspecialty practice and the role of the subspecialist in pediatric residency programs. Teaching residents functional competency in subspecialty areas will have to be more in-depth and will include more curricular time. The need to coordinate the multiple subspecialties' teaching into the standard three-year residency will therefore become more critical and more difficult to achieve.

Finally, support was unanimous for standardizing all recognized pediatric subspecialties. It was proposed that all subspecialties should seek sub-Board status and credentialing. This position is in the interest of maintaining the quality of the educational process and assures at least minimum standards of training in all fields.

The participants also supported convening a broad-based council of individuals to debate these educational issues further and forming a united group so that concrete suggestions might be better implemented in the future. Problems often are clearly delineated and discussed and solutions are proposed at conferences such as this, but then there is no method for implementation. One problem in the past has been that the various pediatric representative groups offer different opinions on an issue in testimony before Congress-a confusing situation. Practicing pediatricians, health maintenance organizations, and the academic community must be brought together so that changes in pediatrics may be better implemented in the future.

Sample Size

George W. Brown, MD

• Before undertaking a research comparison, investigators may wish to estimate the sample sizes needed to assure that the research is feasible and is worth the effort and expense. Such calculations require several decisions by the researchers: (1) the acceptable level of the type I error (P value), (2) the desired power of the test, (3) the difference between the samples that is considered to be important, and (4) the variability expected among the values to be studied. Some recipes for estimating approximate sample sizes are suggested.

(AJDC 1988;142:1213-1215)

A question often asked of statistical consultants by researchers, after a project is finished, is, "What do these numbers mean?" Before a project is begun, a frequent question is, "How large should my samples be?" Discussions of estimation of sample size in introductory statistical texts may discourage some biomedical investigators because of excessive emphasis on theory or too much unfamiliar mathematics.

At the risk of offending statistical purists, I here offer some "cookbook" recipes for estimating sample size for comparisons of two groups. The procedures apply to separate groups of subjects, not to "paired" observations in which each subject is measured under two different conditions.

AVERAGES

One set of recipes is for comparing two averages. In the first situation, the researcher knows in advance which sample will have the larger average. This is called a *one-way test*, because the averages can differ in only one direction. A study on the reduction of hyperbilirubinemia is an example.

The second recipe is for comparisons in which the researcher does not know in advance which average will be higher. This is called a two-way (or two-tailed) test; sample A may have either a larger or a smaller average than B (if they differ).

PROPORTIONS

Comparisons of proportions in two samples also require two recipes. One deals with the one-way situation in which the researcher knows in advance which sample will have the larger proportion of subjects with the event of interest. The other recipe is for comparing proportions when either could be the larger, the two-way situation.

PRELIMINARY DECISIONS

Before attempts at estimating sample size can be meaningful, the research team must make three thoughtful decisions. The first decision concerns the risk of the type I error (also called α) acceptable to the investigator. This is the risk of concluding that an important difference is present, when it is not.1 In practical terms, it is the risk that an observed difference is attributed to an intervention or other factor of interest when the difference is actually due to chance (random) variation among the measurements. The practice of selecting an α level of .05 is widespread among biomedical researchers; this is the familiar P = .05, the critical value for "statistical significance." (This P should be capitalized, because it denotes a probability; lowercase p implies a proportion.)

The second decision by the investigator is the allowable risk of the type II error (β) . This is the error of concluding that an important difference

is not present when it is. It is the risk of missing something important. Some authors express this notion in terms of "power," the complement $(1-\beta)$ of the type II error risk. Power can be thought of as the probability of finding the "important difference" if it exists. The β risk is often ignored in clinical research design and analysis, but it cannot be ignored when sample size calculations are attempted. Investigators often choose power of .80 or .90, ie, β risk of .20 or .10.

The third decision is what difference between averages or proportions is important enough to justify doing the study. Would a reduction in an average serum cholesterol level of 0.2 mmol/L be impressive enough to justify a large, expensive clinical trial? How about 1 mmol/L? What difference in proportions between two samples is "important" enough to repay the cost and effort to demonstrate it? Would a difference of, say, 3% between positive responses to two vaccines be an important difference? This decision, on what is considered "a difference worth searching for," may be the most subtle element needed to estimate sample sizes in clinical studies.

A fourth element must be provided from the knowledge and experience the researchers have about the observations they plan to make. Using past experience, published data, pilot studies, or hunch, the investigator must make a preliminary guess at the standard deviation of the values in the two samples whose averages are to be compared. In dealing with differences between two proportions, the researcher must have at least a rough idea of the magnitude of the proportions that are likely to occur. For example, the investigator should know in advance whether one of the proportions will be near 10% or 50% or 90%.

Two monographs devoted to sample

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| Values for t _s , t _{2s} , or t _{2s} * | | | | | | |
|--|-----|------|-------|-----------------|------|------|
| | | | a, 2a | , or 2 <i>b</i> | | |
| n* | .40 | .20 | .10 | .05 | .02 | .01 |
| 5-15 | .86 | 1.33 | 1.73 | 2.09 | 2.53 | 2.85 |
| 16-26 | .85 | 1.30 | 1.68 | 2.02 | 2.42 | 2.70 |
| 27-35 | .85 | 1.30 | 1.67 | 2.00 | 2.39 | 2.66 |
| 35+ | .84 | 1.28 | 1.65 | 1.96 | 2.33 | 2.58 |

n is the investigator's first guess at a feasible (available?) sample size.

size and power analysis2,3 combine the important difference with the projected "variability" just mentioned. These combinations are called the "effect size" or the "critical effect size." This maneuver reduces the interacting elements from five to four: a level, power, effect size, and sample size.

These reference texts^{2,3} provide guidance to sample-size calculations for a variety of research designs, well beyond the basic comparisons of the two samples discussed here. They emphasize the concepts that underlie calculations of power as well as sample size.

COMPARING TWO AVERAGES Two-way

The investigator does not know in advance whether the average of one sample will be larger or smaller than the average of the other sample.

$$n = 2 (s/d)^2 \times (t_a + t_{2b})^2$$

where n is the number in each sample (this is goal of the recipe); d, the important difference (supplied by the investigator) (Note that the recipe does not require that either one of the averages be known; only the postulated important difference is required.); s, SD expected (supplied by the investigator); t_a for n^* , factor from the Table where a is the α level and n^* is a first guess at a feasible sample size (both a and n^* decided by the investigator); and t_{2b} for n^* , factor from the Table, where b is the β level and n^* is the first guess at a feasible sample size. The subscript 2b means that the t factor is selected from the Table by first doubling the $b(\beta)$ chosen by the researcher, then locating the t factor in the column headed by this doubled b. The n^* is a rough guess as to what sample size might be feasible,

given the realities of the study conditions. (Statisticians will recognize that n^* is related to their poetic but mysterious "degrees of freedom.")

One-way

The direction of the difference between the averages is known before the trial is done.

$$n = 2 (s/d)^2 \times (t_{2a} + t_{2b})^2$$

EXAMPLE

Hemoglobin levels of a group of inner-city children are compared with hemoglobin levels of comparable suburban children. The s of hemoglobin measurements is estimated to be about 15 g/L. The research team decides that finding a difference in average hemoglobin values of at least 10 g/L would be important. An α level of .05 (P=.05) and a β of .10 (power = 90%) are chosen. A first guess at sample size n^* is 50.

Consulting the Table, t_a is 1.96 and t_{2b} is 1.28 (the subscript directs the user to the heading .20, because 2bherein is $2 \times .10$).

$$n=2 (15/10)^2 \times (1.96 + 1.28)^2$$

 $n=47.24$, rounded to 48

If the research team is convinced that the inner-city sample will have lower average hemoglobin levels than the contrast group, the one-way recipe could be used. This produces an n = 39.

Prior knowledge of the direction of the difference of interest allows the two samples to be somewhat smaller. although the researcher's criteria remain the same. That is, α is still .05, β is .10, and d is 10 g/L.

COMPARING TWO PROPORTIONS Two-way

The user has no prior knowledge of which sample will have the larger proportion. Subjects in the two samples are unrelated; they are not the same subjects treated twice.

$$n = 2 \{ (p \times q)/d^2 \} \times (t_a + t_{2b})^2$$
,

where n is the number in each sample; p, the average of the two proportions expected (guessed at by researcher); q, 1-q; d, the important difference between two samples (decided by researcher); t_a for n^* , the factor from the Table where a is α and n^* is the first guess at sample size; and t_{2b} for n^* , the factor where b is β and n^* is guess at sample size.

One-way

The proportion in one sample is known in advance to be higher (or lower) than in the other.

$$n = 2 \{(p \times q)/d^2\} \times (t_{2a} + t_{2b})^2$$

Example

The proportion of toddlers with protective levels of rubella antibodies is evaluated in two communities. The research team considers a difference (d) between the two proportions of 20% to be important to find, if true. Pilot studies suggest that the average proportion of toddlers with protective antibodies is about 60%. The team decides to use α of .01 (P = .01) and β of .05 (power = 95%). There is no prior information as to which community might have the higher proportion of positive subjects, so a two-way calculation is used. Using a first guess of 50 for n^* the Table gives t_a as 2.58 and t_{2b} as 1.65.

$$n = 2\{(.60 \times .40)/.20^2\} \times (2.58 + 1.65)^2$$

 $n = 214.71$, rounded to 215

If the investigators were willing to settle for less power, say .80 instead of .95, the n shrinks to 141 in each sample. That is, when the research team is willing to accept a greater \$\beta\$ risk, smaller samples can be used. In practical terms, a power of .95 means that, if the selected d is true, it will be found in 19 of 20 trials (all else being equal). With a power of .80, the rate of success is reduced to four trials in five.

Statisticians will object to the loose idea of guessing at an "average p" in the $p \times q$ numerator. Suppose the true average p were .50 instead of the .60 used. This would change n to 147 instead of 141, not a large error. The safest practice is to favor guesses at average p near .50; this tends to assure that the calculated n is large enough to avoid too small samples in actual practice.

COMMENT

The procedures suggested are for comparing two samples, both free to vary in accord with the properties of small samples drawn from large populations. These recipes are not appropriate for estimating the size of a

1. Brown GW: Errors, type I and II. AJDC 1983;137:586-591.

2. Cohen J: Statistical Power Analysis for the Behavioral Sciences. Orlando, Fla, Academic Press Inc, 1977.

3. Kraemer HC, Thiemann S: How Many Subjects? Statistical Power Analysis in Research.

single small sample to be compared with a universe whose mean and variability are known or, in the case of proportions, compared with a large population whose characteristics are well defined.

The theoretical background for the recipes offered can be found in many statistics textbooks,⁴⁻⁷ but the formulas given here are less rigorous than those recommended in textbooks. Investigators who plan to examine repeated observations on the same subjects or who must use samples that

References

Beverly Hills, Calif, Sage Publications Inc, 1987.
4. Dixon WJ, Massey FJ Jr: Introduction to Statistical Analysis, ed 4. New York, McGraw-

Hill International Book Co, 1983.
5. Fleiss JL: Statistical Methods for Rates and Proportions, ed 2. New York, John Wiley & Sons Inc. 1981 are not of equal size should consult a statistician for guidance.

CAVEAT

Statisticians and others familiar with data analysis may be offended by the oversimplifications presented. On the other hand, perhaps judicious simplification will reassure clinical investigators in their contemplation of sample sizes and may make biomedical researchers more comfortable in discussing these issues with their statistical consultants and with each other.

6. Fleiss JL: The Design and Analysis of Clinical Experiments. New York, John Wiley & Sons Inc, 1986.

7. Sokal RR, Rohlf FJ: Biometry, ed 2. New York, WH Freeman & Co, 1981.

Book Review

A Parent's Guide to Spina Bifida, by Beth-Ann Bloom and Edward Seljeskog, 104 pp, with illus, \$14.95, Minneapolis, University of Minnesota Press, 1988.

A Parent's Guide to Heart Disorders, by James H. Moller and William A. Neal, 163 pp, with illus, \$14.95, Minneapolis, University of Minnesota Press, 1988.

These volumes are the first in a series from the University of Minnesota titled *Guides to Birth and Childhood Disorders*. The series, edited by Robert J. Gorlin, offers a uniformity and comprehensiveness not found in similar texts. Individual volumes are modeled after the collaborative efforts of David W. Smith and Ann Asper Wilson, coauthors of the highly successful *The Child With Down's Syndrome*.

The authors, editors, and advisory board have produced concise, informative, and current texts. The guides include important factual data presented clearly. The authors simplify etiologies and clarify complicated procedures, giving parents and families a better understanding of complex issues. Important social issues are addressed, including education and sexuality (in the spina bifida text)

and exercise limitations and death (in the heart disorders text). Photographs of technical equipment help to demystify treatments and interventions. Useful appendixes include a dictionary of medical terms, a glossary of roles and training of various medical professionals, and listings of national associations and suggested readings. The dust jacket and book design are cheerful and attractive.

Forthcoming topics in this welcome series include cerebral palsy, cystic fibrosis, kidney disorders, leukemia, sickle cell anemia and thalassemia, and spine disorders. I will recommend these guides to parents and families, and I am confident that pediatricians, family practitioners, and nurse-practitioners working with children with chronic illnesses will find them very useful adjuncts to their practices.

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Institutional Screening for the Fragile X Syndrome

Randi Hagerman, MD; Rebecca Berry, MS; A. W. Jackson III; Julianne Campbell, RN; Ann C. M. Smith, MA; Loris McGavran, PhD

 Cytogenetic screening of mentally retarded patients for the fragile X (fra[X]) chromosome is helpful in identifying Individuals who could benefit from genetic counseling and treatment. Previous studies have demonstrated a prevalence of the fra(X) syndrome as high as 6% in institutionalized retarded males. The physical and behavioral predictors of positive findings from cytogenetic testing have not been clarified, since many features of the fra(X) syndrome are found in other retarded populations. We performed physical and cytogenetic examinations on 440 patients at the Wheat Ridge (Colo) Regional Center. Twenty-eight (6.3%) demonstrated abnormal karyotypes. Seventeen of these were autosomal abnormalities or sex chromosome aneuploidies and 11 demonstrated the fra(X) chromosome (seven males, four females). In males, the physical features that were predictive of the fra(X) syndrome included the combination of ear lengths of 7.0 cm or greater, macroorchidism of 30 mL or greater, and the presence of hand calluses or lesions secondary to hand biting. The fra(X) chromosome was not seen in spastic quadriplegic patients. All seven males with the fra(X) syndrome were detected among the 141 ambulatory males who resided in the highest functioning units at this institution.

(AJDC 1988;142:1216-1221)

The prevalence of retardation secondary to the fragile X (fra[X]) syndrome is approximately one in 1300 people,1,2 with a carrier frequency of approximately one in 750.3,4 This identifies the fra(X) syndrome as the most common familial cause of mental retardation known. Appropriate cytogenetic evaluations to identify patients have only been available in the United States and most of the world in the 1980s. Therefore, most individuals with the fra(X) syndrome have not yet been identified. The identification of individuals who have the syndrome is important for genetic counseling of other affected and carrier family members and for medical treatment and specialized education of affected individuals.5.6 Institutional screening has been performed in the past with a prevalence of the fra(X) syndrome ranging from 1.6% to 6.2% in mentally retarded males (Table 1). The prevalence in institutions seems to be similar to the prevalence found in a population screening of severely retarded boys in a Swedish county, where 6% were fra(X) positive,9 and in England, where 9% of severely retarded boys were fra(X) positive.10

The expense and effort involved in screening an entire institution has stimulated more selective screening within institutions (Table 2). Brøndum-Nielsen et al,11 Howard-Peebles and Finley,12 Primrose et al,13 and others have focused on males with macroorchidism and they have demonstrated that 4% to 39% of these males are fra(X) positive. Previous studies have excluded additional physical features that singularly or in combination with macroorchidism may help to identify institutionalized patients who are at high risk for the fra(X) syndrome. It is also unclear whether the fra(X) phenotype is unique compared with other physical features of institutionalized patients.

We undertook the screening of patients in our local state institution for the retarded to identify the prevalence of the fra(X) syndrome. We also wanted to characterize the occurrence of features on physical examination that are associated with the syndrome and that may differentiate males with the fra(X) syndrome from other institutionalized retarded males. The clarification of predictive features will ultimately be helpful for future highrisk screening.

PATIENTS AND METHODS

The Wheat Ridge (Colo) Regional Center is one of three state institutions for the mentally retarded in Colorado. From 1983 to 1986, there were 533 patients residing at the center: 80% of the patients were white (non-Hispanic), 13% Hispanic, 6% black, and 1% Oriental. The ages ranged from 4 to 69 years, with a mean age of 26.4 years. Eighty patients demonstrated a medically documented cause of their retardation, including a specific syndrome, chromosomal abnormality, or central nervous system trauma, and were therefore not cytogenetically screened. This included 24 patients with trisomy 21 and one with deletion of the short arm of chromosome 5. An additional 13 patients were not screened because of lack of permission or refusal to cooperate with the drawing of a blood sample. The remaining 440 patients (267 males and 173 females) underwent a brief physical assessment and cytogenetic testing.

Physical Assessment

A physical examination was performed to evaluate the presence or absence of physical signs associated with the fra(X) syndrome. ¹⁴ The physical features reported herein include ear length (measured in centimeters from the top to the bottom of the pinna [Fig 1]) and testicular volume (measured with an orchidometer). When

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| | Donaletton | No. of Patients | |
|----------------------------------|--|---------------------------------------|------------------------------------|
| Source, y | Population Studied, Location | With Fra(X)* Syndrome/ No. Studied | Frequency of Fra(X) Syndrome, % |
| Sutherland, ⁷ 1982 | All mentally retarded males without known chromosomal disorder from three institutions, Australia | 7/444 | 1.6 |
| Jacobs et al,37 1983 | Mentally retarded males on community placement from an institution, Hawaii | 5/274 | 1.8 |
| Froster-Iskenius et al,* 1983 | All mentally retarded males were screened—even those with known chromosomal abnormality, Northern Germany | 15/242 | 6.2 |
| Arinami et al.38 1986 | All mentally retarded males without other known chromosomal abnormalities, Japan | 13/243 | 5.3 |
| Arinami et al,39 1987 | All mentally retarded females without other known chromosomal abnormalities, Japan | 2/190 | 1 |

^{*}Fra(X) indicates fragile X.

| C | Population | No. of Patients With Fra(X)* Syndrome/ | Frequency of |
|---------------------------------------|--|--|--------------------|
| Source, y | Studied, Location | No. Studied | Fra(X) Syndrome, % |
| Kähkönen et al,⁴⁰ 1981 | 150 mentally retarded males without dysmorphic features or major malformations, Finland | 6/150 | 4 |
| Brøndum-Nielsen et al," 1982 | Of 178 institutionalized males, 52 had macroorchidism, Denmark | 2/52 2/178 | 4 1.1 |
| Carpenter et al,41 1982 | 50 males grouped with and without a family history of mental retardation, United States | 5/50 | 10 |
| Howard-Peebles and Finley, 12 1983 | Of 444 institutionalized males, 28 had macroorchidism, United States | 7/28 7/444 | 39 1.6 |
| Kirkilionis et al,42 1983 | 818 males without Down's syndrome and 167 males with macroorchidism, Canada | 18/167 18/818 | 11 4 |
| Fryns et al, ⁴⁹ 1984 | 1223 mentally retarded males from eight institutions; only those considered clinically normal were examined cytogenetically, Belgium | 57/354 57/1223 | 16 4.7 |
| Trusler and Beatty-De Sana,⁴ 1985 | Of 380 mentally retarded patients, 43 were randomly selected and 23 were referred for fra(X) evaluation, United States | 5/43 12/23 | 12 52 |
| Sanfilippo et al,45 1986 | Of 450 mentally retarded residents, 91 males were selected, Italy | 4/91 | 4.4 |
| Primrose et al, ¹³ 1986 | Of 512 mentally retarded males, 100 were randomly selected without other diagnosis; 61 patients had macroorchidism, but only 30 received cytogenetic studies; 70 males had family history of mental retardation, England | 7/100 8/30 24/70 39/512 | 7 27 34 8 |

^{*}Fra(X) indicates fragile X.

the testicle was larger than the largest ellipse of the orchidometer (25 mL), the length (L), and width (W) were measured with a tape measure and the testicular volume was calculated using the equation $V=\pi/6$ L×W². The hands and forearms were also inspected for calluses, scars, or other lesions resulting from self-mutilation.

Cytogenetic Evaluations

Chromosomal studies of peripheral blood lymphocytes were performed on all patients who underwent a physical examination. Samples of whole blood from each patient were inoculated into both McCoy's modified medium supplemented with 15% fetal bovine serum and medium 199 supple-

mented with 5% fetal bovine serum. Each medium was adjusted to a pH of 7.6. After 72 hours, 5-fluoro-2'-deoxyuridine (FUdR) was added to the McCoy's cultures to a final concentration of 10-7 mol/L. Cells from both cultures were harvested after 96 hours of incubation and G-banded preparations were analyzed for the presence of structural abnormalities and the fra(X) chromosome. 16,17 Autosomal fragile sites were observed to confirm the efficacy of this technique for inducing fragility. At least 100 cells per patient were examined. A second blood sample was obtained whenever the original sample demonstrated abnormalities. For patients who had structural autosomal defects, the second sample was cultured using high-resolution techniques. Parental chromosomes were stud-

ied whenever the parents were available. For all patients who demonstrated the fra(X) chromosome in less than 3% of the metaphases examined, repeated testing was performed on a second sample. Additional family members were contacted for all individuals who were fra(X) positive. If a patient demonstrated a low percentage of fra(X)-positive cells (<3%), they were considered positive only if the fra(X) chromosome was present on repeated testing and if other family members, when available, also demonstrated the fra(X) chromosome.

RESULTS

Of the 440 patients screened, 28 patients (6.3%) demonstrated abnor-

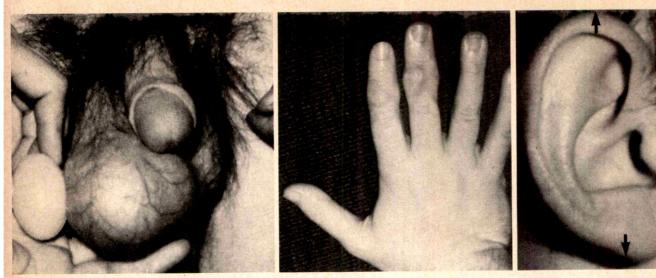


Fig 1.—Left, Macroorchidism with bilateral testicular volume of 100 mL compared with 25-mL volume of orchidometer. Center, Hand calluses secondary to hand biting. Right, Ear length was measured in centimeters from top to bottom of pinna (arrows).

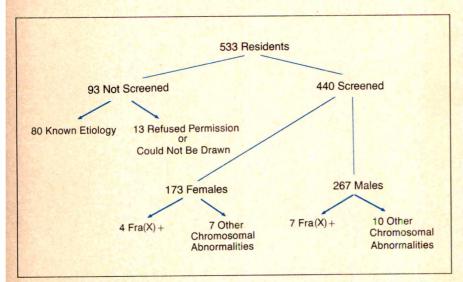


Fig 2.—Flow chart for positive findings in this institutional screening. Fra(X) indicates fragile X syndrome.

mal karyotypes. Seventeen were structural autosomal abnormalities or sex chromosome aneuploidies that are listed in Table 3. Eleven patients (2.5%), seven males and four females, demonstrated the fra(X) chromosome (Table 4 and Fig 2). Two males were low expressors cytogenetically, but on subsequent samples they demonstrated the fra(X) chromosome and other family members were also affected and demonstrated the fra(X) chromosome in a higher percentage of cells. All of the females were low expressors, repeatedly demonstrating 1% to 2% of cells that were positive for the fra(X) chromosome. In two females, parents were available for study and one mother was also cytogenetically positive in one of 100 cells but was unaffected. In all four females, no other affected individuals were known by history and no other family members were available for study.

An analysis of the predictive physical features was performed only on the males because of the inclusion of testicular measurements and because the fra(X) diagnosis could not be confirmed in other family members in the females. Of the 267 males examined, 92 (34.5%) demonstrated a bilateral ear length of 7.0 cm or longer. Most of these ears were subjectively considered to be prominent. This ear length is greater than 2 SDs above the mean for the children and young adult population. 18-20 However, only four (4.3%) of the males with long ears were fra(X) positive. The patients who were fra(X) positive did not demonstrate malformed or cauliflower ears.

Macroorchidism was defined as testicular volume of 30 mL or larger for postpubertal patients and above the 95th percentile for prepubertal and pubertal patients. 18,21 Bilateral macroorchidism was seen in 36 (13.5%) of the males examined, and all were postpubertal. Six (16.7%) of males with macroorchidism were fra(X) positive.

Hand or forearm lesions secondary to self-mutilation were seen in 36 (13.5%) of males and five (13.9%) of these males were fra(X) positive. Only 17 (6.4%) of males had large ears and macroorchidism and four (23.5%) of these males were fra(X) positive. Only eight (3.0%) males had all three features, large ears, macroorchidism, and hand lesions, and four (50%) were fra(X) positive (Fig 3). The fra(X) chromosome was not seen in spastic quadriplegics or in bedridden or wheelchair-bound patients. All seven males who were fra(X) positive were

| Case No. | Karyotype | Unusual Physical Features |
|----------|---|--|
| 1 | 46,X,derX,t(1;X) (q32;q26.1) | Large ears |
| 2 | 46,XY,t(2;16)* | Macrocephaly, hyperkeratosis |
| 3 | 46,XX,del(3) (25.3) | Spastic quadriplegia |
| 4 | 46,XX,4p — | None |
| 5 | 46,XY,4q+ | Spastic quadriplegia, prominent ears |
| 6 | 46,XY,5p — | Spastic quadriplegia, long narrow face |
| 7 | 46,XY, -5, + der5,t(5;8) (5p15.31;8p21.3)mat | Large ears |
| 8 | 46,XY,del(8) (p23.1) | Epicanthal folds, low-set ears, high palate, simian creases, hyperpigmentation |
| 9 | 46,XX,inv dup(8) (q22 qter) | None |
| 10 | 46,XX,11q- | None |
| 11 | 46,XX, probable inv dup(14) (pter q32.3::q13 q32.3::qter) | Hyperpigmented callouses, right hemiparesis, asymmetric face |
| 12 | 45,XY, -14, -21 + robt(14;21) (cen;cen)* | Dental malocclusion |
| 13 | 46,XX,inv dup(16) (16q13 q22.3) | High palate, widow's peak, dental malocclusion |
| 14 | 46,XY,del(18) (q21.31) | None |
| 15 | 46,XY,18q+ | Large ears |
| 16 | 47,XXY | Cryptorchidism, spastic quadriplegia |
| 17 | 47,XY, + dicentric satellited fragment of unknown origin | Large ears, pectus excavatus |

^{*}Cases 2 and 12 appear to be balanced translocations with no discernible loss of euchromatin. Parents were unavailable in both cases, so it is unknown if these rearrangements were de novo.

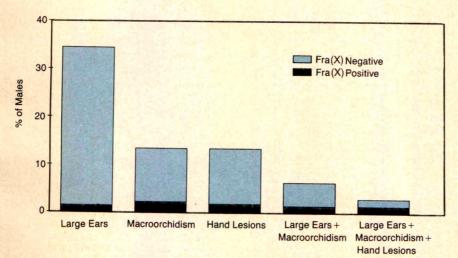


Fig 3.—Occurrence of individual and combined physical features in 267 males screened. FraX indicates fragile X syndrome.

detected among the 141 ambulatory males at this institution who resided in the highest functioning units where patients excelled in self-care.

COMMENT

This study has demonstrated that physical features associated with the fra(X) syndrome, including large ears, macroorchidism, and hand calluses, are common among institutionalized

males. When they are looked for in combination, however, the chance of identifying an individual who is fra(X) positive increases significantly. The expense of a cytogenetic analysis has inhibited widespread screening, at least in the United States, although the expense may be justified by the money saved in preventing future affected individuals through genetic counseling.²² The combination of large ears, macroorchidism, and the pres-

ence of hand calluses has yielded 50% of the patients who are fra(X) positive in our institution, although three of seven patients who were fra(X) positive did not have all three features. With limited financial resources, however, one may consider initiating a screening project with a combination of features that predict the highest yield and then focusing on individual features such as macroorchidism or hand calluses, which have a yield from 16.7% to 13.9% in this study. All of the males with the fra(X) syndrome were found among 141 ambulatory patients and none of the bedridden or severely spastic quadriplegics were fra(X) positive. If screening efforts were focused on ambulatory institutional patients the yield would be approximately 5% fra(X) positive. Previous studies have demonstrated institutional prevalences that vary from 1.6%7 to 6.2%8 (Table 1), and this variance may depend on the type and severity of retardation in patients in each institution. Clearly, patients with the fra(X) syndrome are ambulatory (unless an additional problem exists) and from our experience they frequently do well in a sheltered workshop setting and in a

L

| Patient No. | Cytogenetic Studies | Physical Signs | Family History‡ |
|----------------|------------------------|--|---|
| 1 | 31/100 | Long narrow face, macroorchidism, calluses on hands | Maternal cousin is mentally retarded and fra(X) + |
| 2 | 40/100 | Long narrow face, macroorchidism, self-mutilation but no calluses on hands | Brother is mentally retarded and fra(X) + |
| 3 | 20/100 | Long narrow face, macroorchidism, large ears, hand calluses | Sister and mother are fra(X) + |
| 4 | 22/100 | Macroorchidism, large ears, hand calluses | Brother is mentally retarded and fra(X)+ |
| 5 | 1/100, 3/100 | Macroorchidism, large ears, hand calluses | Brother is mentally retarded and two sisters are fra(X) + |
| 6 | 22/100 | Macroorchidism, large ears, hand calluses | Brother is fra(X) + |
| 7 | 1/100, 2/300 | Long face, scoliosis, self-mutilation but no calluses | Mother and two sisters are fra(X) + |

*At Wheat Ridge (Colo) Regional Center.

†The fraction listed represents the number of cells demonstrating the fra(X) chromosome (numerator) over the total number of cells examined (denominator). Where two fractions are listed, the results of repeated evaluations are included also.

‡The results of fra(X) testing on family members are listed: fra(X) + indicates the fra(X) chromosome has been demonstrated cytogenetically in the family members.

community living situation, such as a group home. There may be an even higher prevalence of individuals that are fra(X) positive in such settings compared with an institutional population. Thake et al23 have conducted a similar analysis of predictive physical features in a community study of 156 boys with severe mental retardation. They found an overall prevalence of 9%, which is higher than that found in institutional studies. The presence of a head circumference over the 50th percentile, a testicular volume over the 50th percentile, and an IQ between 35 and 70 improved the chance of finding a male with the fra(X) syndrome to one in every 3.6 studied who had all three findings.28

For each individual who is identified in screening, a pedigree can then be ascertained and often additional affected males and heterozygous females can be identified. The relatives are often numerous, and genetic counseling services are essential for these individuals.24,25 Amniocentesis is available,26,27 and the use of DNA probes can be helpful in identifying heterozygotes and in prenatal diagnosis.28,29

Treatment is an additional reason for identifying individuals with the fra(X) syndrome. Although specific interventions have not been clearly beneficial for adult males with the fra(X) syndrome, prepubertal males and females who are identified in the pedigrees may be helped by medical and educational interventions. 14,28 Stimulants³⁰ and other medication^{6,14} can decrease hyperactivity and attentional problems in prepubertal males with the fra(X) syndrome. The specific pattern of cognitive deficits and the sensory integration deficits in children with the fra(X) syndrome can be addressed educationally and in language and occupational therapy. 14,31,32

An additional benefit of cytogenetic screening for the fra(X) chromosome is the identification of other autosomal or sex chromosomal anomalies. It is imperative that all the chromosomes be studied in a fra(X) analysis. In this study, 17 abnormalities were detected, although two seemed to be balanced translocations without missing genetic material. However, parents were unavailable for study in these two cases and therefore the significance of their translocations in respect to their phenotype could not be clarified (Table 4).

When this project was initiated in 1983, we eliminated all previously known chromosomal disorders and other syndromes. However, the fra(X)syndrome has been diagnosed in patients with Down's syndrome,33 and Klinefelter syndrome,34 where it may be associated with nondisjunction,33 and in other disorders such as neurofibromatosis,35 where it is probably a chance association. Future screens should not necessarily eliminate patients with a known diagnosis.

Four females were detected who demonstrated only one or two cells

with the fra(X) chromosome of 100 to 200 metaphases examined. Although the background breakage near the fra(X) site may be of the order of one per 100 cells, 36 all females who were fra(X) positive demonstrated the fra(X) chromosome on repeated cytogenetic evaluations. We consider the four low expressing females as presumptively demonstrating the fra(X) syndrome, but this cannot be confirmed by family studies and they were excluded from the analysis of predictive features. In general, we recommend repeated cytogenetic analysis of low expressors, and family studies if the fra(X) chromosome is observed in more than one sample.

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In Other AMA Journals

JAMA

Documentation of an AIDS Virus Infection in the United States in 1968 R. F. Garry; M. H. Witte; A. A. Gottlieb; M. Elvin-Lewis; M. S. Gottlieb; C. F. Witte; S. S. Alexander; W. R. Cole; W. L. Drake, Jr (JAMA 1988;260:2085)

Reduced Platelet Count as a Risk Factor for Intraventricular Hemorrhage

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 The role of thrombocytopenia as a risk factor for intraventricular hemorrhage in infants of very low birth weight is unclear. This study investigates the relationship between the lowest platelet count and the occurrence of intraventricular hemorrhage in 302 consecutively admitted infants with birth weights under 1500 g. Intraventricular hemorrhage, which occurred in 90 infants (29.8%), was correlated with the lowest platelet count obtained during the first 4 days of life. In 27 infants with intraventricular hemorrhage, the lowest platelet count was less than 100 × 10°/L. Statistical analysis of the data demonstrated that reduced platelet count was not associated significantly with intraventricular hemorrhage. Similarly, the severity of intraventricular hemorrhage did not correlate with the lowest platelet count. These data suggest that a reduced platelet count does not play a major role in the pathogenesis of intraventricular hemorrhage in infants of very low birth

(AJDC 1988;142:1222-1224)

Many factors have been implicated in the pathogenesis of intraventricular hemorrhage (IVH) in the preterm infant.^{1,2} However, the role of reduced platelet count in this context remains unclear. Thus, several studies have suggested a direct relationship between low platelet count and the occurrence of IVH,³⁻⁶ whereas others have failed to demonstrate this association.^{7,8} In the light of this controversy, the purpose of this study is to determine the role of reduced platelet counts in the genesis of IVH in a large population of infants of very low birth weight (VLBW).

METHODS Patient Population

The patient population comprised 302 infants with birth weights less than 1500 g who were admitted consecutively to the Neonatal Intensive Care Unit at British Columbia's Children's Hospital, Vancouver, during a period of 18 months. The mean gestational age was 27.5 weeks (range, 23 to 35 weeks) and the mean $(\pm SD)$ birth weight was 1076 ± 246 g. Infants were admitted during the first day of life and received standard treatment in terms of ventilation, circulatory support, and parenteral nutrition. The following variables, which have been implicated in the pathogenesis of IVH, were recorded: birth weight, mode and location of delivery, condition at delivery, respiratory distress, perinatal asphyxia, presence or absence of pneumothorax, and outcome. Perinatal asphyxia was defined as a fetal scalp or an umbilical cord pH of less than 7.2, or Apgar scores under 3 at one minute or under 6 at five minutes, or all of these. Four patients with platelet counts less than $20 \times 10^{9}/L$ received platelet transfusions. Indomethacin sodium trihydrate was administered to two patients only during the first 4 days of life for the treatment of symptomatic patent ductus arteriosus and was not used prophylactically.

Diagnosis of IVH

Intraventricular hemorrhage was diagnosed by routine ultrasound scanning on days 4 and 14 of life with a mechanical sector scanner (Diasonics ADA 400) equipped with a 7.5-MHz transducer. Scans were performed by a radiologist who was unaware of the infant's platelet count. The IVH was graded as I to IV according to the system of Papile et al,° adapted for use with ultrasound scanning. Grades III and IV were considered to represent severe IVH.

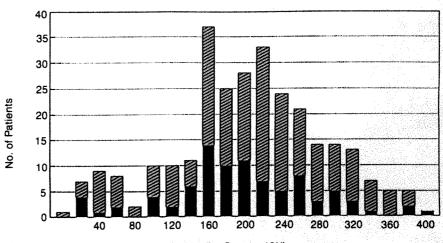
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Platelet Count × 10°/L

Distribution of lowest platelet count and intraventricular hemorrhage. Solid bars indicate presence of, and striped bars, absence of, intraventricular hemorrhage.

| Table 1.—Correlation of Intraventricular Hemorrha | ge (IVH) With Lowest |
|---|----------------------|
| Platelet Count* | |

| | | | Lowest Platel | elet Count × 10°/L | | |
|-------------------|---------------------------------|------------------|---------------------|---------------------|-------------------|--|
| Patie | No. of Patients (n = 302) | <100 (n = 27) | 100-150 (n = 26) | 151-200 (n = 72) | >200 (n = 177) | |
| Present Absent | 90 212 | 7 20 | 9 17 | 27 45 | 47 130 | |

 $[\]chi^2 = 3.41$, df = 3; P = .33.

Table 2.—Correlation Between Grade of Intraventricular Hemorrhage (IVH) and Lowest Platelet Count*

| | Lowest Platelet Count × 10°/L | | | | |
|----------------------------|-------------------------------|------------------|---------------------|---------------------|-------------------|
| IVH | No. of Patients (n = 302) | <100 (n = 27) | 100-150 (n = 26) | 151-200 (n = 72) | >200 (n = 177) |
| Absent | 212 | 20 | 16 | 46 | 130 |
| Present Grades I and II | 40 | 2 | 4 | 11 | 23 |
| Grades III and IV | 50 | 5 | 6 | 15 | 24 |

^{*} $\chi^2 = 0.47$, df = 1; P = .5.

| | | | | et Count × 10°/L | |
|-----------------|---------------------------|------------------|---------------------|---------------------|-------------------|
| Birth Weight, g | No. of Patients (n = 302) | <100 (n = 27) | 100-150 (n = 26) | 151-200 (n = 72) | >200 (n = 177) |
| <750 | 32 | 6 | 5 | 4 | 17 |
| 750-999 | 84 | 7 | 7 | 23 | 47 |
| 1000-1499 | 186 | 14 | 14 | 45 | 113 |

 $[\]chi^2 = 8.57$, df = 6; P = .199.

| Table 4.— | -Correlation Bet | tween Perinata | I Asphyxia and | Lowest Platel | et Count* |
|---------------------------------------|------------------|----------------|----------------|------------------|-----------|
| | No of | TO BELLE | Lowest Platel | et Count × 10°/L | 2 Tak |
| Perinatal Patients Asphyxia (n = 302) | <100 | 100-150 | 151-200 | >200 | |
| | (n = 27) | (n = 27) | (n = 69) | (n = 179) | |
| Present | 88 | 12 | 9 | 21 | 46 |
| Absent | 214 | 15 | 18 | 48 | 133 |

 $[*]x^2 = 4.15$, df = 3; P = .246.

Platelet Counts

Blood samples were obtained by puncture of the prewarmed heel or from an indwelling arterial catheter. Platelet counts were performed on all infants at the time of admission and repeated daily on all sick infants in whom the lowest platelet count (LPC) had been noted between 2 and 4 days of age.⁶ Platelet counts were performed on an electronic cell counter (Coulter S Plus IV). Platelet counts less than 30×10^9 /L were confirmed by manual chamber counts using phase-contrast microscopy. The LPC measured during the first 4 days of life was used in subsequent analysis.

Statistical Analysis

Results were analyzed statistically in terms of absolute platelet count and by stratification, using the χ^2 test, the Student t test, and progessive logistic regression.

RESULTS

Intraventricular hemorrhage occurred in 90 (29.8%) of the 302 infants. In 40 infants, the IVH was grade I or II, and in 50 infants, it was grade III or IV. As has been reported previously, IVH occurred before age 4 days in most instances. 2.10-12

Platelet counts were measured on

the first day of life in all infants and were repeated between age 2 and 4 days in 215 infants (71%) who had medical complications. In 27 infants (9%), the LPC was less than 100×10^{9} /L; in 26 infants (9%), the LPC was between 100 and 150×10^{9} /L; and in 72 infants (24%), the LPC was between 151 and 200×10^{9} /L. In the remaining 177 infants (59%), all platelet counts were greater than 200×10^{9} /L.

The distribution of the LPC in the entire study population and in the infants who developed IVH is displayed in the Figure. There was no apparent difference between the incidence of IVH in infants with platelet counts less than 100, 100 to 150, and 150 to 200 × 109/L as compared with the incidence in the remaining infants (Table 1). To avoid assumptions concerning a minimum "safe" platelet count, variances of the LPC in infants both with and without IVH were examined by the Student t test. There was a similarity of LPC in infants in each group (F' = 1.23, P > F' = .278), indicating the absence of a direct relationship between the LPC and the occurrence of IVH. A stepwise logistic regression procedure was performed to allow for interactions between dependent variables that might mask a possible effect of thrombocytopenia on the risk of IVH due to other variables. Three variables (severity of respiratory distress, pneumothorax, and birth weight) were found to have a significant influence on the incidence of IVH. After allowing for the effect of these factors, other variables, eg, LPC, perinatal asphyxia, serum sodium level, and location of delivery, were not significant (P = .05).

The relationship between the LPC and severity of IVH was examined (Table 2). Severe IVH, ie, grades III and IV, was not associated with a higher incidence of reduced platelet counts than mild IVH, ie, grades I and II ($\chi^2=0.47$, df=1; P=.5). Furthermore, there was no significant association between reduced platelet count and birth weight (Table 3). The relationship between the LPC and perinatal asphyxia is demonstrated in Table 4. Although there was a trend toward lower platelet counts in infants

who sustained perinatal asphyxia, this did not reach statistical significance.

Assessment of the power of the study demonstrated that a 14% decrease of low platelet counts in infants with IVH would have been detected with a β error of 0.1 (α = 0.05), indicating that the study population was sufficiently large to detect any clinically significant decrease in reduced platelet counts in infants with IVH.

COMMENT

These data do not demonstrate a clear association between reduced platelet count and IVH, an observation that is in contrast to several recent reports.3-6 Thus, Beverley et al,3 in a study of coagulation status in 106 infants of less than 34 weeks' gestation, observed significantly lower platelet counts at 48 hours of age in infants with IVH. However, these data do not permit conclusions as to whether the low platelet counts were a cause or consequence of IVH. Similarly, McDonald et al' reported a significantly higher incidence of IVH in 50 infants of gestational ages less than 33 weeks in whom platelet counts were less than $150 \times 10^{\circ}/L$ within the first 8 hours of life. In a study of 58 VLBW infants. Setzer et als observed a relationship between mean platelet counts in the first day of life and IVH in 71%. However, when adjusted for the effect of perinatal asphyxia, this relationship was no longer statistically significant.

Finally, in a study of VLBW infants born in one year in whom the incidence of IVH was 56%, an increased incidence and severity of IVH was observed in infants in whom platelet counts were less than $100 \times 10^{9}/L$ within the first 2 weeks of life.6 However, in this study, thrombocytopenic infants were compared with "sick controls." Thus, although two studies3,6 have identified major differences between infants with and without IVH in terms of factors such as birth asphyxia and severity of respiratory disease, multivariate analysis was not performed to determine whether these variables could explain the apparent association between platelet count and IVH. Our study, as well as others that use multivariate analysis, have failed to demonstrate a significant association between IVH and platelet counts. 7.8 The conclusions from our data are similar whether or not multivariate analysis is applied.

Additional factors may produce a noncausal association between thrombocytopenia and IVH in this context. Thus, an increased risk of IVH with perinatal asphyxia has been reported. ^{5,13-15} However, because perinatal asphyxia may cause a consumptive coagulopathy, it may result in both IVH and thrombocytopenia, which may create an apparent association between the two variables. Second, in this study, platelet counts were repeated more often in the sicker infants

thrombocytopenia in the sickest infants, ie, those who are at highest risk for IVH from any cause. Third, it has been demonstrated that hemorrhage itself may result in consumption of platelets. 16 Consequently, infants who have sustained IVH may have lower platelet counts following the hemorrhage.

The lack of association between IVH and reduced platelet count in our

after the first day of life. Thus, there

is a greater likelihood of detecting

The lack of association between IVH and reduced platelet count in our study population, despite various factors that would tend to emphasize a positive relationship, argues against a role for reduced platelet count in the pathogenesis of IVH. Because of the small number of infants with an LPC of less than 50×10^9 /L, we were unable to establish whether such very low counts are related causally to IVH. Other variables, eg, methods of blood collection, location, and mode of delivery, may explain the differences in incidence of thrombocytopenia between various studies. ¹⁵

The lack of a causal relationship between reduced platelet count and IVH suggests that treatment of moderate thrombocytopenia (>50×10⁹/L) is unlikely to decrease the incidence of IVH in infants of VLBW.

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Safety and Efficacy of Flexible Endoscopy in Children With Bronchopulmonary Dysplasia

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• Because concern has been raised about the efficacy and safety of flexible fiberoptic bronchoscopy (FFB) in pediatric patients with chronic cardiopulmonary disorders, we reviewed the resuits of 129 flexible endoscopies performed on 47 children with a history of bronchopulmonary dysplasia (BPD) at our institution over a 44-month period. Indications for FFB; weight and age of the patient; and procedure format, including medication usage, findings, specimen results, and complications. were analyzed. Evaluation of previously diagnosed subglottic stenosis and airway abnormalities were the two most common indications (33% and 32%, respectively). Persistent or recurrent infiltrates or atelectasis, need for cultures, stridor, failure to extubate, hoarseness. and persistent wheeze were also cited. Endoscopic diagnoses included adenoidal hypertrophy, laryngomalacia, vocal cord abnormalities, interarytenoid membrane, subglottic stenosis, granulomas, tracheobronchomalacia, stenosis, obstruction, generalized inflammation/ edema, polyps, tracheal bronchi, and anomalous bronchial anatomy. Cytomegalovirus, pneumococcus, nontypeable Haemophilus influenzae, Pseudomonas, or mixed gram-negative flora were isolated from some patients without tracheostomy. Minor complications (transient bradycardia, mild nasopharyngeal bleeding, and mild worsening of upper airway obstruction) occurred in 3.1% of procedures, but no severe complications occurred. Management was directly affected by procedure results in 41% of procedures. We concluded that the FFB can be a safe, useful procedure in the management of children with BPD. (AJDC 1988;142:1225-1228)

Flexible fiberoptic bronchoscopy (FFB) has long been an effective tool in the diagnosis and management

of airway abnormalities in adults. Despite the need to sedate small children and the large size of the bronchoscope relative to the infant airway, FFB is a frequently used diagnostic modality in pediatrics. It has been suggested that there are no absolute contraindications to FFB, except when information can be obtained in a better way.1 Recently, Wagener² reported a death following FFB and bronchoalveolar lavage (BAL) in a 2-year-old child with laryngomalacia, congestive heart failure, and pulmonary hypertension. He concluded that severe cor pulmonale with congestive heart failure resulting from chronic upper airway obstruction is a contraindication to passing the bronchoscope below the site of obstruction. Furthermore, procedures such as BAL should be avoided in children with pulmonary hypertension.2

Infants and small children requiring prolonged periods of mechanical ventilation and oxygen therapy as neonates for respiratory distress syndrome may develop bronchopulmonary dysplasia (BPD) with resultant cor pulmonale, congestive heart failure, and airway abnormalities. Although these patients may frequently benefit from direct observation of the airway via FFB, their possible increased risk of complications from the procedure led us to review our experience to determine the safety and efficacy of FFB in children with a history of BPD.

PATIENTS AND METHODS

The records of all patients with BPD who underwent FFB and/or laryngoscopy at Rainbow Babies and Childrens Hospital, Cleveland, from January 1984 to August 1987 were reviewed. Bronchopulmonary dysplasia was defined as a neonatal respiratory disorder requiring mechanical ventilation and/or supplemental oxygen for at least the first 30 days of life. All children had clinical or roentgenographic pulmo-

nary abnormalities consistent with BPD, such as tachypnea, retractions, wheezing, hypoxemia, persistent or recurrent infiltrates, atelectasis, or hyperinflation. Clinical history, indications for FFB, weight and age of the patient, procedure format, medication usage, findings at FFB, specimen results, and complications were analyzed.

In the 44-month study period, 129 flexible procedures were performed on 47 different patients. The age and weight characteristics at the time of procedure are shown in the tabulations below:

| | NO. (%) OI |
|-----------|------------|
| Age | Children |
| <3 mo | 19 (14.7) |
| 3-<6 mo | 12 (9.3) |
| 6-<9 mo | 12 (9.3) |
| 9-<12 mo | 14 (10.9) |
| 12-<18 mo | 17 (13.2) |
| 18-<24 mo | 22 (17.0) |
| 2-3 y | 25 (19.4) |
| >3 v | 8 (6.2) |

The mean $(\pm SD)$ age was 17.1 ± 12.4 months.

No (0%) of

| | 140. (70) 01 |
|------------|--------------|
| Weight, kg | Children |
| 1-<2 | 12 (9.3) |
| 2-<3 | 10 (7.7) |
| 3-<5 | 19 (14.7) |
| 5-<10 | 49 (38.0) |
| 10-20 | 38 (29.5) |
| Unknown | 1 (0.8) |

The mean $(\pm SD)$ weight was 7.2 ± 2.9 kg.

Thirty-four percent of procedures were done on an outpatient basis. Thirty-two percent of procedures were done in children weighing less than 5 kg. Patients varied in degree of respiratory dysfunction. Although accurate assessments were not recorded for each procedure, 13 patients were supported by mechanical ventilation, 11 with supplemental oxygen, and one by nasal continuous positive airway pressure during the study period. Cardiac status was documented by an electrocardiogram and/or echocardiogram in 37 patients. Twenty (54%) had right atrial enlargement and/or right ventricular hypertrophy. In four of these patients, significant biventricular hypertrophy was noted. Two other patients had isolated left ventricular hypertrophy. A coarctation of the aorta and

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right atrial thrombus was documented in two other children. Acute deterioration in respiratory status, uncontrolled congestive heart failure, or bleeding diathesis were clear contraindications of FFB. During all or part of the study period, 23 (49%) of 47 patients had a tracheostomy.

Of the 129 procedures, 18 were solely laryngoscopies and the remainder were tracheobronchoscopies. A flexible bronchoscope (Olympus 3C4, Olympus Corp, Lake Success, NY) (3.5-mm diameter) was used alone or in conjunction with an ultrathin fiberscope or ultrathin flexible bronchoscope (Machida America, Orangeburg, NY). Whenever possible, a video recording (Olympus OTV-E) of the procedure through the bronchoscope was made. All procedures were performed by one of five experienced pediatric bronchoscopists in either a specially equipped bronchoscopy suite or the intensive care unit.

A transnasal and/or tracheostomy approach was taken in all but one (transoral) procedure. The patient was not allowed to eat or drink for several hours, and in most cases intravenous access was secured before the procedure. Each child was swaddled in a sheet for restraint. After achieving adequate sedation and topical anesthesia, the stomach was aspirated with a suction catheter. If the patient tolerated this, the flexible bronchoscope was advanced through the same nostril. After adequate inspection of the nasopharynx, epiglottis, arytenoid cartilages, and surrounding structures, the vocal cords were anesthetized with a lidocaine hydrochloride solution sprayed through the suction channel of the bronchoscope. The tip was then advanced into the subglottic space and, if patent, farther into the trachea and lower airways. Whenever possible, in intubated patients or in those with a tracheostomy, the bronchoscope was passed through the tube or stoma to examine the distal trachea before proceeding with the transnasal approach. Cardiac monitoring and 100% "blowby" oxygen during procedures were routinely performed. The time spent evaluating the lower airway was specifically dependent on the patient's ability to tolerate the procedure. In general, this part of the procedure lasted less than 15 minutes

During the 44-month period, 22 patients were evaluated only once; ten patients, twice; and five patients, on three separate occasions. Endoscopy was performed on ten children four or more times. Evaluation of previously diagnosed subglottic stenosis and tracheostomy evaluation were the two most commonly reported indications (43 [33%] of 129 and 41 [32%] of 129, respectively). These diagnoses were made repet-

| Table 1.—Methods | of Sedation With Dosage Range | s er franklig |
|---|-------------------------------|---------------------|
| Route and Medication | Dosage | % of Total Cases |
| Intrarruscular Meperidine hydrochloride: promethazine hydrochloride | 2:1 mg/kg | |
| Meperidine:promethazine: chlorpromazine hydrochloride | 2:1:1 mg/kg | 29 (total) |
| Intravenous | 0 5 0 5 maka | 15 |
| Meperidine | 0.5-2.5 mg/kg, total dose | |
| Diazepam | 0.3-0.75 mg/kg | 1.5 |
| Meperidine:diazepam | 1:0.1-2:0.6 mg/kg | 4 |
| Methohexital sodium | 0.5-0.75 mg/kg/dose | 2 |
| Oral | | |
| Chloral hydrate | 25-100 mg/kg | 7 |

itively in some children. Other indications included persistent or recurrent infiltrates/ atelectasis in 24 (19%) of 129, stridor in 13 (10%) of 129, prolonged intubation or failure to extubate in six (5%) of 129, hoarseness or voice abnormalities in six (5%) of 129, wheezing in four (3%) of 129, cyanotic or obstructive episode in four (3%) of 129, hemoptysis in four (3%) of 129, cough in three (2%) of 129, upper airway obstruction in two (1.5%) of 129, to rule out tracheoesophageal fistula in two (1.5%) of 129, and to rule out foreign body in one (0.8%) of 129 patients. In 19 (15%) of 129 patients, the need for cultures (bacterial, viral, acidfast bacillus, and fungal) was listed as an indication.

Lidocaine was the sole agent used as a mucosal anesthetic. Twenty-one patients under 12 months of age received a total dose of 2.5 mL/kg or less of 1% lidocaine hydrochloride. All others received a total dose of 2.5 mL/kg or less of 2% lidocaine hydrochloride. In 18 procedures, 0.2 mL (at 1:10 000) of topical epinephrine administered nasally (for vasoconstriction) was used in conjunction with the lidocaine. In five cases, atropine (0.01 to 0.15 mg/kg) was given intravenously to control excess secretions.

Sedation was used in 74 cases (57%) by a number of different methods (Table 1). Intramuscular sedation with meperidine hydrochloride and promethazine hydrochloride with or without chlorpromazine hydrochloride (Thorazine) was used in 38 procedures (29%). Intravenous meperidine was used as the sole agent in 19 procedures (15%) and intravenous diazepam in two procedures (1.5%). The combination of the two agents meperidine and diazepam was used in six cases (4%). Intravenous methohexital sodium (Brevital) was used in three procedures (3%), and oral chloral hydrate was used as the sole agent of sedation in nine cases (7%). Additional

sedation was required with chloral hydrate or intravenous sedation in eight cases (11% of cases in which sedation was used).

Bronchoalveolar lavage was performed in 19 patients with inflammation or atelectasis. Total volume of normal saline ranged from 0.8 mL/kg to 4.9 mL/kg. No greater than 5-mL lavage volumes were used at any one time with 50% to 70% of the volume typically recovered.

RESULTS

Findings from FFB are summarized by airway location in Table 2. A total of 169 endoscopic diagnoses were made in the 47 patients. Upper airway abnormalities noted included intranasal erosions, adenoidal hypertrophy, laryngomalacia, vocal cord abnormalities (granulomas, paresis), and redundant epiglottis. Although subglottic stenosis was diagnosed in 52% of children with tracheostomies vs 64% of children without tracheostomies, the degree of subglottic stenosis was more severe in the former group. The incidence of tracheomalacia was greater in the tracheostomy group (52% vs 36%). Bronchomalacia and tracheobronchial stenosis/obstruction were diagnosed with the same frequency in the two groups. An unsuspected right tracheal bronchus was noted in two patients with persistent right upper lobe infiltrates. Lower airway granulomas and granulation tissue were found in a much higher frequency in patients with a tracheostomy vs those without a tracheostomy (65% vs 4%, respectively), possibly the result of trauma from vigorous suctioning with a catheter. Other findings included intraluminal polyps, generalized air-

Table 2.—Patients With Specific Endoscopic Diagnoses Grouped by Anatomical Location

| | | No. (%) o | f Patients | |
|-------------------------------------|-------------------------|--------------------------|------------|---------------------------|
| Diagnosis | Trache | Vith eostomy = 23) | Trache | thout eostomy = 24) |
| Supraglottic | | La Salada | | |
| Intranasal erosions | 0 | | 1 | (4) |
| Adenoidal hypertrophy | | (35) | 1 | (4) |
| Laryngomalacia | 2 | (9) | 9 | (38) |
| Redundant epiglottis | 0 | | 1 | (4) |
| Interarytenoid membrane | 0 | | 1 | (4) |
| Pharyngeal collapse | 5 | (22) | | (21) |
| Glottic | | THE STEP AND | | R GER |
| Vocal cord abnormalities | 4 | (17) | 5 | (21) |
| Subglottic | | | | B LOW |
| Subglottic stenosis | 12 | (52) | 16 | (64) |
| Tracheal Tracheomalacia | 10 | (52) | | (0.0) |
| Tracheomegaly | | | | (36) |
| Extrinsic tracheal | The Late of the Late of | (4) | 0 | |
| compression | 2 | (9) | 1 | (4) |
| Tracheobronchial stenosis/bronchial | | (43) | | (29) |
| R-sided tracheal bronchus | 0 | | 2 | (8) |
| Bronchial | THE RESIDENCE | NAME OF TAXABLE PARTY. | | |
| Granulomas/granulation | 15 | (65) | 1 | (4) |
| Bronchomalacia | 7 | (30) | 9 | (38) |
| Polyps | 1 | (4) | 2 | (8) |
| Inflammation/edema | 5 | (22) | | (29) |
| Miscellaneous bronchial findings* | 2 | (9) | | (21) |
| Normal lower airway | | (4) | | (4) |

^{*}Included fibrous adhesions, mucus plugging, anomalous anatomy, or bronchorrhea.

way inflammation/edema, external compression, mucus plugging, and distal bronchorrhea. The lower airway was normal in only two patients.

Specimens for bacterial culture were obtained in 16 cases. Four of these patients had a tracheostomy at the time of BAL. Culture results from seven patients were unremarkable. Heavy growth of pneumococcus or nontypeable Haemophilus influenzae was documented in five patients. The culture of one patient who did not have a tracheostomy yielded Pseudomonas and mixed gram-negative flora. Viral cultures were performed in seven patients, and cytomegalovirus was recovered in one instance. No other viral respiratory pathogens were isolated. One patient with a tracheostomy had a positive culture for Candida albi-

The results of flexible endoscopy had a direct effect on further manage-

ment in 41% of procedures. Tracheostomy tube changes were performed under endoscopic visualization in 31 procedures. By guiding changes in tracheostomy tube size, type, or orientation (after cutting and remolding the tube tip), endoscopy allowed for prompt resolution of tube obstruction from granulation tissue or segmental tracheomalacia. Following 17 other procedures, patients were referred directly to surgery for procedures (two for tracheostomy, 11 for degranulation, two for adenoidectomy, and one for laryngotracheoplasty with a cartilaginous stent). In five cases, after postural drainage failed, lavage of atelectatic areas resulted in prompt clinical and/or roentgenographic improvement.

Complications were noted in four of the 129 procedures. One infant developed bradycardia during FFB that responded immediately to ventilation

with bag, mask, and 100% oxygen following temporary cessation of the procedure. One patient developed mild nasopharyngeal bleeding that resolved spontaneously, and another had increased stridor after FFB, which responded to a single racemic epinephrine aerosol treatment. The fourth patient, a 32-month-old 13.5-kg male child with a history of severe tracheomalacia and upper airway obstruction and who had received 30 mg of meperidine hydrochloride (2.5 mg/kg) and 7.5 mg of diazepam (0.6 mg/kg) intravenously before the procedure, developed moderately severe respiratory distress from upper airway obstruction secondary to voluminous secretions and poor pharyngeal tone after FFB. His condition responded to treatment with naloxone hydrochloride, oxygen by mask, and racemic epinephrine aerosol. None of the four patients had a tracheostomy at the time of FFB, and no apparent complications were associated with BAL.

COMMENT

The advantages of FFB over rigid bronchoscopy in pediatric pulmonary medicine have previously been summarized by Wood and Postma. 1,4 Although a rigid bronchoscope is essentially a metal endotracheal tube, the flexible bronchoscope is more like a steerable suction catheter. The distal end of the flexible instrument can be extended or flexed to guide the bronchoscope into the desired airway location. This capability and a slightly smaller outside diameter give the flexible bronchoscope a greater peripheral field for inspection. Rigid bronchoscopy is usually performed with the patient under general anesthesia in an operating room. Flexible bronchoscopy usually requires topical anesthesia and sedation and thus can be performed at the bedside if necessary. Because there is generally no need for assisted ventilation or general anesthesia, dynamic airway abnormalities, such as tracheobronchomalacia, can be better assessed with FFB.

The American Thoracic Society guidelines for FFB in adults state that in all clinical situations the risk of FFB must be weighted against the potential benefits for each patient.⁵ Several of the increased risks (lack of patient cooperation, partial tracheal bronchial unstable obstruction, asthma, respiratory insufficiency associated with moderate hypoxemia or any degree of hypercarbia, pulmonary hypertension, debility, and malnutrition) stated in the guidelines could apply to infants and children with BPD. Although several authors have documented the safety and efficacy of FFB in infants and small children with a variety of respiratory signs and symptoms, 4,6,7 similar data on a population of pediatric patients with underlying chronic cardiopulmonary disorders do not exist in the literature.

Wood and Postma1 have suggested that stridor, atelectasis, recurrent or persistent pneumonia, persistent wheezing, hemoptysis, suspected foreign-body aspiration, tracheostomy evaluation, and difficult intubations be considered specific indications for en-Likewise. examination. doscopic Nussbaum⁶ has included specimen collection for cultures and cytology in cases of persistent pulmonary infiltrates. Patients with BPD, therefore, might benefit from direct airway examination if the incidence and severity of risks were low enough.

In our study, endoscopy was clearly helpful in a large percentage of these patients. In addition to the 41% of procedures in which management was directly affected by results, other conditions were identified that could have affected therapy. Over 30% of our patients had tracheobronchomalacia. Infants with tracheobronchomalacia may present with persistent wheezing, which is often misdiagnosed as reactive airway disease. Typically, this wheezing does not respond to bronchodilator or steroid therapy, and if it is severe enough it may require positive end-expiratory pressure.8 Two of our patients had an anomalous tracheal bronchus that was unsuspected before bronchoscopy. This finding may be responsible for recurrent infiltrates and diverse respiratory signs and symptoms. In some children, resection of the tracheal bronchus with the segment of the lobe it supplies can lead to dramatic clinical improvement.9

The number and severity of complications in our review agree favorably with reports in the literature. In Nussbaum's series of 164 bronchoscopies in infants and children aged 1 day to 16 years with unresolved pneumonia, persistent atelectasis, or stridor, three children experienced mild transient stridor after the procedure and five children had mild nasopharyngeal bleeding controlled by local application of epinephrine (5% complication incidence).8 Two episodes of transient hemoptysis and one episode of transient hypoxemia were noted after FFB in 95 pediatric patients in the series of Fitzpatrick et al.7

Several factors might explain our overall success in this group of pediatric patients. All decisions to perform FFB are made by experienced bronchoscopists after carefully weighing the risks and benefits in each case. All procedures, whenever possible, are performed in a fully equipped bronchoscopy suite adjacent to the intensive care unit. Special precautions are routinely taken. A minimum staff of three, including the bronchoscopist and bronchoscopy nurse, is present throughout the procedure. We now routinely use pulse oximetry to monitor oxygen saturation throughout the procedure. Procedures are performed with minimal time spent in the lower airway, and no greater than 5 mL/kg of normal saline in 5-mL aliquots is used for lavage. Examination is aided by a video system allowing the operator to review findings with no risk to the patient. In addition, all patients are monitored for at least one hour after the procedure by our bronchoscopy nurse or other trained personnel until sedation has dissipated.

Medication usage for sedation varied greatly in this study as well as in the literature. In children with BPD, undersedation may lead to unacceptable arterial oxygen desaturation because of ventilation/perfusion mismatch, intrapulmonary shunting, or breath holding. Oversedation may exacerbate upper airway obstruction, especially in patients with mild pharyngeal hypotonia. There appears to be no consensus as to an optimal regimen in pediatric FFB. Nussbaum⁶ used 1 mg/kg of meperidine hydrochloride and 1 mg/kg of chlorpromazine hydrochloride intramuscularly 45 minutes before endoscopy. In the study of Fitzpatrick et al,7 all procedures were performed in an operating room bronchoscopy suite. Intravenous diazepam or meperidine (dosages not specified) was used in 17% of cases. General anesthesia was used in 32% of cases.6 The methods of sedation used in our study varied based on the bronchoscopist's preference. The establishment of optimally defined sedation practices might further reduce complication rates.

Our experience demonstrates the safety and usefulness of flexible endoscopy in evaluating upper and lower airway problems in children with a history of BPD when performed by experienced operators under controlled circumstances. This procedure is not presently a routine part of the evaluation of these patients at our institution. No more than 10% of patients fitting the definition of BPD that we selected ever undergo FFB.

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The best treatment to kill lice and nits

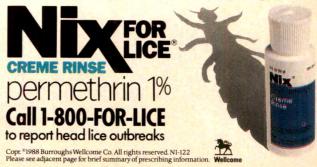
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CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day oraily) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp. Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic or other reasons.

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Figure 1.



Figure 3.



Figure 2.



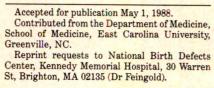


Figure 4.



Denouement and Discussion

Epidermolytic Hyperkeratosis

Fig 1.—Infant at age 4 hours showing rapidly desquamating skin with raw, denuded, weeping patches.

Fig 2.-Infant at 1 week of age.

Fig 3.—At age 4 months skin becomes less erythematous and more hyperkeratotic.

Fig 4.—Patient's mother's skin. Note thick, grayish brown to black scales.

Manifestations

Epidermolytic hyperkeratosis, previously designated as bullous congenital ichthyosiform erythroderma, is a rare form of ichthyosis. Manifestations are usually present at birth. The epidermis is thick and macerated, resembling a wet blotter. Portions of skin may have already been desquamated in sheets, leaving raw, denuded, weeping patches. These findings are characteristic of a burned baby rather than a colloidion baby. The thick, macerated membrane rapidly sheds, leaving a raw, moist, tender surface that may resemble the skin present in other diseases in which blistering is present. Bullae are the most characteristic manifestation of the disease, and their presence differentiates epidermolytic hyperkeratosis from the other types of ichthyosis. The recurrent bullae usually last throughout childhood, become less prominent with time, and may resolve in early adolescence. Occasionally, bullae may be present in adults. The face is frequently less severely affected than other areas of the body. During the newborn period, because of the blistering and denudation, patients are at high risk of developing dehydration, hypothermia, and sepsis.

As the child matures, thick, grayish brown to black scales cover the skin surface and are most prominent in the intertriginous areas. Palms and soles show various degrees of hyperkeratosis. The scales are small and dark, and may appear as tiny ridges. Patches of scales shed and form islands of relatively nonhyperkeratotic skin. However, the scales reappear relatively rapidly. Bacterial overgrowth in the hyperkeratotic stratum corneum epidermidis causes an unpleasant odor. Pruritus is a variable feature. Ectropion is not present in this type of ichthyosis, and the hair, eyes, teeth, and nails are usually normal.

Histologic findings are diagnostic. There is marked hyperkeratosis with a thick, granular zone. Papillomatosis and acanthosis are characteristic but variable. Extensive vacuolization of cells in the midepidermis and in the granular layer leads to clefts that form small, irregular cavities. Bullae are intraepidermal. The differential diagnosis includes other bullous disorders present in the neonatal period, includ-

ing impetigo bullosa, staphylococcal scalded skin syndrome, and epidermolysis bullosa. When blistering is not a prominent component, the other ichthyotic dermatoses, usually lamellar ichthyosis, should be considered.

Genetics

This condition is inherited in an autosomal dominant manner.

Treatment

Epidermal denudation can result in extensive insensible water loss, resulting in dehydration and hypothermia that require treatment. There is also a high risk of sepsis occurring, requiring appropriate antibiotic therapy. Radiant warmers increase the insensible water and heat loss and should not be used.

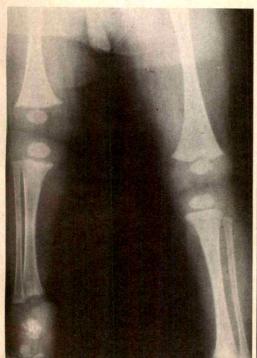
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Radiological Case of the Month

Kazimierz Kozlowski, MD, Edward H. Bates, MD (Contributors); Lionel W. Young, MD (Editor for This Case); Beverly P. Wood, MD (Section Editor)



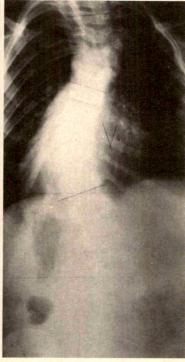


Figure 1.









A 12½-year-old girl, whose condition was correctly diagnosed at birth, was seen in orthopedic consultation for right limb shortening that had been present since infancy (Fig 1). She had developed a thoracic abnormality that was managed with operative vertebral fusion when she was 4 years old and again when she was 9 years old.

On physical examination, this prepubertal, well-nourished, mentally normal girl measured 152 cm in height. She had spotty cicatricial alopecia (Fig 2, far left). Her right leg was 9.4 cm shorter than the left one (6.4 cm in the femur and 3 cm in the tibia). Her right foot was about one size smaller than the left foot. She walked on tiptoe with her right foot in an extreme equinus position (Fig 2, left center). In the right limb flexures at the wrist (Fig 2, right center), elbow, and knee (Fig 2, far right), there were linear cicatricial or erythematous areas with thick scales; they tended to wax and wane.

No ocular anomalies were present on physical examination.

There was no family history of similar abnormalities.

Accepted and edited for publication by Lionel W. Young, MD, former section editor, April 29, 1987. From the Department of Radiology, Randwick Medical Center and Royal Alexandra Hospital for Children, Sydney, Australia.

Reprint requests to Department of Radiology,

Reprint requests to Department of Radiology, Children's Hospital Medical Center of Akron, 281 Locust St, Akron, OH 44308 (Dr L. W. Young).

Denouement and Discussion

Dominant X-linked Chondrodysplasia Punctata

Fig 1.—Left, Roentgenogram of legs at age 10 months shows shortening of long bones of right lower leg. Note punctate calcification of right tarsal bones. Right, Roentgenogram of trunk at age 12½ years shows thoracic scoliosis.

Fig 2.—Far left, Photograph of back of head shows focal, cicatricial alopecia. Left center, Full frontal photograph shows shortening of right leg. Right center, Photograph of right wrist shows ichthyosiform lesions. Far right, Photograph of right knee flexure shows linear, depigmented cicatricial lesions.

Dominant sex-linked chondrodysplasia punctata was delineated as a separate entity by Happle¹ in 1977. It is assumed that at least one fourth of all cases of chondrodysplasia punctata are sex-linked. The disease is characterized by a triad of asymmetrical skeletal, ocular, and skin anomalies.

Skeletal anomalies are those of more or less severe chondrodysplasia punctata at birth. Later, when the punctate calcifications have been resorbed, the radiologic diagnosis of the condition may be uncertain. The vertebral findings consist of vertebral malsegmentation with scoliosis. The limb findings may be hypoplastic/dysplastic tubular bones and joints, talipes equinovarus, and, rarely, hexodactyly (Fig 1).^{2,3}

The most common ocular anomalies are unilateral or bilateral congenital

cataracts. Other eye abnormalities such as microphthalmia, microcornea, glaucoma, dislocated lenses, rubeosis iridis, posterior and anterior synechiae, and atrophy of the retina and optic nerve also have been sporadically reported.⁴

Skin anomalies show variable and changing patterns. In newborns, they are described as erythroderma, ichthyosis, or ichthyosiform erythroderma. The inflammatory skin findings regress in the following weeks or months, leaving spotty or linear areas of atrophoderma, hyperkeratosis, and pigment anomalies, particularly on the forearms and lateral parts of the chest (Fig 2, left center and right center). 1.5

Hair anomalies are constant findings. The hair, which is partly normal and partly coarse, lacks luster, and patchy areas of cicatricial alopecia are constant findings (Fig 2, far right).

Ear and nail anomalies also have been reported.

The right limb problems of this patient were managed orthopedically.

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Radiological Case of the Month

Bruce A. Schroeder, MD, David J. Czarnecki, MD, Robert G. Wells, MD, John R. Sty, MD (*Contributors*); Lionel W. Young, MD (*Editor for This Case*); Beverly P. Wood, MD (*Section Editor*)

Accepted and edited for publication by Lionel
W. Young, former section editor, May 18, 1987.
From the Department of Radiology, Children's
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Schroeder, Wells, and Sty), and St Luke's Hospital

tal, Milwaukee (Dr Czarnecki). Dr Schroeder is now with the Department of Radiology, Children's Memorial Hospital, Omaha.

Reprint requests to Department of Radiology, Children's Hospital Medical Center of Akron, 281 Locust St, Akron, OH 44308 (Dr L. W. Young). A 6-year-old boy was found by his parents with his neck trapped under an automatically controlled garage door. Cardiopulmonary resuscitation was immediately instituted by the parents. After stabilization and ventilatory assistance, the patient was transferred to Children's Hospital of Wisconsin in Milwaukee. At the time of

admission, the patient was comatose with fixed and dilated pupils. Numerous contusions and petechiae were noted over his cheeks and orbits. Cranial computed tomography was performed both with and without intravenous contrast medium enhancement (Figs 1 and 2).



Figure 1.

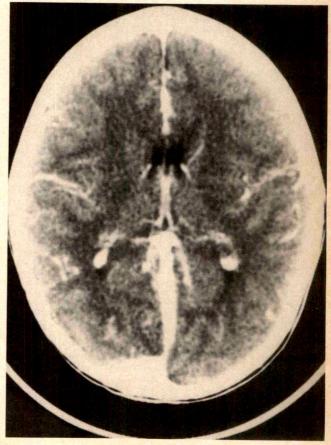


Figure 2.

Denouement and Discussion

Poststrangulation Cerebral Sinovenous Thrombosis

Fig 1.—Plain computed tomographic scan of head at level just above basal ganglia shows linear midline focus of increased attenuation representing clotted blood in Galen's vein and straight sinus.

Fig 2.—Contrast-medium—enhanced computed tomographic scan shows even greater attenuation of Galen's vein and enhancement of straight sinus and proximal right transverse sinus secondary to dural sinus collaterals.

Cerebral sinovenous thrombosis has been classified as being either septic or aseptic. Septic thrombosis is secondary to inflammation involving the intracranial venous system, as in meningitis and encephalitis, or from intracranial spread from mastoiditis or sinusitis. Aseptic causes are many (eg, polycythemia vera, trauma, strangulation, dehydration, congenital heart disease, collagen vascular disease, and oral contraceptive use), and rarely does this condition occur as an isolated finding without an identifiable cause.1 The exact incidence of cerebral sinovenous thrombosis is uncertain; however, it probably occurs more frequently than diagnosed. Dependent on the location of the occlusion, clinical and usually nonspecific manifestations include headache, seizures, altered state of consciousness, nausea and vomiting, coma, and hyperpyrexia. More specific focal neurologic deficits have also been described.¹

When thrombosis occurs, computed tomographic (CT) findings show increased attenuation in Galen's vein and the straight and transverse sinuses. This hyperdensity is due to formation of a recent blood clot. After intravenous injection of contrast medium, CT scans show contrast medium enhancement in the straight and transverse sinuses, which is thought to be caused by increased flow through dural collateral venous channels.

Cerebral sinovenous occlusion is associated with a high mortality ranging from 40% to 81%. 2.3 This patient ultimately died of complications of severe cerebral edema with uncal herniation. The medical examiner's office decided that this case was accidental

and an autopsy consequently was not performed.

Early recognition of cerebral sinovenous occlusion and appropriate therapy are essential to improve survival and to decrease related morbidity. Computed tomographic findings are usually pathognomonic, as in this case. If the CT findings are equivocal, an angiogram may be needed to confirm the diagnosis.⁴

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Effect of Calcitonin Replacement Therapy in Idiopathic Juvenile Osteoporosis

Elizabeth C. Jackson, MD; C. Frederic Strife, MD; Reginald C. Tsang, MD; Harold K. Marder, MD

An 8-year-old boy with idiopathic juvenile osteoporosis and multiple fractures had three abnormalities of bone mineral metabolism: calcitonin deficiency, elevated serum calcitriol concentrations, and hypercalciuria. Calcitonin deficiency was documented by two attempts to stimulate calcitonin secretion with intravenous calcium and pentagastrin. Treatment for 11 months with daily subcutaneous injections of human calcitonin and oral administration of calcitriol failed to reduce the excessive bone resorption observed on bone biopsy, and the fracture rate did not decrease. Treatment was discontinued for two months, then resumed with calcitonin injections and oral calcium supplementation. The fracture rate decreased but bone biopsy continued to show excessive resorption. Therapy was discontinued. After the onset of puberty, endogenous calcitonin was detectable. Exogenous calcitonin therapy may have failed to control bone resorption for several reasons: insufficient dose, reduction of bone receptors from longterm calcitonin exposure, secondary hyperparathyroidism, or lack of association between calcitonin deficiency and the bone disease.

(AJDC 1988;142:1237-1239)

I diopathic juvenile osteoporosis (IJO) is a rare condition occurring in previously healthy preadolescent children. Excessive bone resorption associated with a negative calcium balance leads to osteoporosis and multiple fractures, characteristically

of the vertebrae and long-bone metaphyses. Serum calcium and phosphorus concentrations are normal. Although the condition heals spontaneously in conjunction with sexual maturation, exogenous estrogen and androgen therapies have not been beneficial. Care of fractures and early ambulation have been the accepted methods of treatment.

We report the clinical course, measurement of hormones governing bone mineral metabolism, and results of bone histomorphologic examination of one patient with LJO who was considered to have calcitonin deficiency and who received a trial of calcitonin replacement therapy.

PATIENT REPORT

An 8-year-old previously healthy boy was referred to an orthopedist for evaluation of a limp. Both parents and seven siblings were in good health. On physical examination the patient's height and weight were at the 90th percentile for age, and he had no stigmas of osteogenesis imperfecta. Roentgenograms showed generalized osteoporosis, an old fracture of the left talus, and avascular necrosis of the left second metatarsal head.

Initial laboratory values included normal thyroid, adrenal, and renal function test results and normal urinary amino acid excretion. Tests of bone mineral metabolism, outlined in Table 1, revealed three abnormalities: hypercalciuria, an elevated serum calcitriol concentration, and undetectable serum calcitonin level. A bone biopsy without tetracycline labeling showed attenuated trabeculae and, under polarized light, excessive remodeling. Osteoid seams were wider than normal, but no marrow fibrosis was detected.

MATERIALS AND METHODS

Serum calcium and phosphorus concentrations were measured by spectrophotometry, and alkaline phosphatase concen-

tration was measured by enzymatic assay (DuPont ACA, DuPont Corp, Wilmington, Del). Parathyroid hormone (PTH) was measured by radioimmunoassay using antibodies to the intact molecule. Measurement of vitamin D metabolites was performed as reported previously.2 Urinary calcium was measured using a spectrophotometer (Bio-Science Laboratories, Van Nuys, Calif). Bone mineral analysis was performed by direct single-beam photon absorptiometry of the nondominant distal one third radius2 and is reported as the number of SDs from the normal mean bone density for age. Calcitonin assays were performed by radioimmunoassay using antiserum recognizing the entire molecule.*

Bone biopsies were performed either with a trephine or by surgical wedge section of the iliac crest. The first specimen was decalcified and evaluated by routine microscopy. The next three biopsies (5, 11, and 24 months after presentation) were performed after tetracycline labeling 21 and seven days before biopsy. (Undecalcified bone was placed immediately in 70% alcohol and shipped to the Bone Mineral Laboratory, Henry Ford Hospital, Detroit, for interpretation by A. M. Parfitt, MD.)

Calcitonin administration was approved by the Human Investigations Committee, and informed consent was obtained from the parents.

RESULTS Observation Before Treatment

As outlined in the Figure, the child was observed for six months without therapeutic intervention. During that period, he had five new fractures associated with minimal trauma. Serum calcitonin concentration remained undetectable despite attempts to stimulate it with calcium and pentagastrin (Table 2). The initial serum level of calcitriol was elevated. Urinary calcium excretion was elevated on three occasions. A second bone biopsy performed six months after the diagnosis showed an extremely abnormal woven

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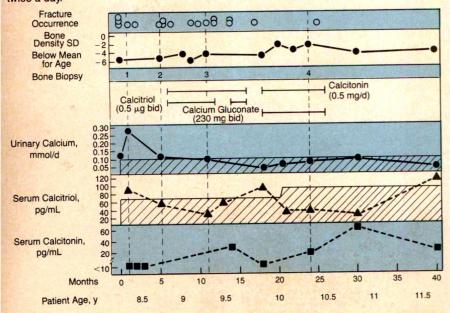
Reprint requests to Department of Pediatrics, University of Kentucky Medical Center, 800 Rose St, Lexington, KY 40536 (Dr Jackson).

| Laboratory Values | Patient | Normal Range |
|---------------------------|---------|--------------|
| Serum calcium, mmol/L | 2.40 | 1.20-2.74 |
| Phosphorus, mmol/L | 1.60 | 0.97-1.94 |
| Alkaline phosphatase, U/L | 22.7 | 2-10 |
| Parathyroid hormone, U/mL | 42 | <150 |
| Calcitriol, pg/mL | 91 | 0-73 |
| Calcifediol, ng/mL | 41 | 11-68 |
| Calcitonin, pg/mL | <10 | <10-107 |
| Urine calcium, mmol/L | 0.11 | < 0.01 |

| Intravenous Infusion | Time, min | Calcium, mmol/L | Calcitonin pg/mL |
|-------------------------|--------------|--------------------|---------------------|
| | (0 | 2.25 | <10 |
| | 30 | 2.9 | <10 |
| Calcium, 8 mg/kg | 60 | 2.52 | <10 |
| | 120 | 2.10 | <10 |
| | 240 | 2.22 | <10 |
| | (0 | 2.40 | <10 |
| | 1 | 2.30 | <10 |
| Pentagastrin, 0.5 μg/kg | 2 | 2.28 | <10 |
| omegaam, rie pama | 3 | 2.32 | <10 |
| | 5 | 2.38 | <10 |

*In this laboratory, mean basal calcitonin in adults is 32 pg/mL, with a range of less than 10 to 107 pg/mL.³ After pentagastrin stimulation in adults, calcitonin rises a mean of 20.4 pg/mL over baseline. Carey et al⁴ report that mean calcitonin concentration in children is 41 pg/mL, with a mean rise over baseline of 146 pg/mL after calcium infusion and 34 pg/mL after pentagastrin infusion.

Fracture incidence, evaluation, and treatment over 40 months in child with idiopathic juvenile osteoporosis and calcitonin deficiency. Figure shows relationship of fractures (open circles) to timing of bone biopsies at 1, 5, 11, and 24 months after presentation. Medications, dosage, and duration of treatment are outlined in fourth line of Figure. Serum calcitrol (triangles) and serum calcitonin (squares) seemed to vary inversely. bid indicates twice a day.



bone, which, in retrospect, was probably extracted from an occult fracture site.

Treatment With Calcitonin and Calcitriol

The continuation of fractures in association with undetectable serum calcitonin concentration prompted therapeutic intervention with 0.5 mg of human calcitonin (Cibacalcin, CIBA-GEIGY, Summit, NJ) subcutaneously every day. Serum calcitonin concentration was detectable during this time, as seen in the Figure. Calcitriol (Rocaltrol, Roche, Nutley, NJ) (0.5 µg, twice a day) was administered to prevent calcitonin-induced hypocalcemia. During 11 months of treatment, we did not observe a decrease in the incidence of fractures. One episode of hypercalcemia responded to withdrawal of calcitriol therapy. After six months of therapy a third bone biopsy showed normal bone formation, increased bone resorption, and very low total bone volume.

Treatment With Calcitonin and Oral Calcium Supplementation

Therapy was discontinued for two months. Serum calcitonin concentration was again undetectable. Because the lack of response to calcitonin and calcitriol therapy might have been due to high calcitriol concentrations, calcitriol therapy was omitted and therapy was resumed with 0.5 mg of human calcitonin daily and 500 mg oral calcium supplementation daily. During this second treatment period the fracture rate decreased; however, the fourth bone biopsy continued to show excessive bone resorption. Total bone volume was slightly improved due to a small increase in bone formation. Despite normal serum calcium and PTH concentrations and normal tubular reabsorption of phosphate, the biopsy revealed qualitative changes of hyperparathyroidism. On admission for his fourth biopsy at age 10 years 4 months, he was noted to be at Tanner stage II in sexual maturation.

Observation After Therapy

All therapy was then discontinued because there was no decrease in osteoclastic activity. No further fractures have been observed. Endogenous basal serum calcitonin concentrations were 62 pg/mL and 23 pg/mL at three and ten months, respectively, after discontinuation of calcitonin therapy. After 40 months of observation and apparent resolution of fractures, bone mineral content remained low at 4.1 SDs below the mean for the patient's age. His growth continued to be excellent, with his height at the 90th percentile.

COMMENT

The course and presentation of our patient are consistent with IJO. He presented with generalized idiopathic osteoporosis, which improved clinically at the time of puberty. In addition to osteoporosis this child had calcitonin deficiency, hypercalciuria, and elevated serum calcitriol concentrations for his age.

Calcitonin inhibits osteoclastic bone resorption and decreases renal tubular calcium reabsorption. ^{5,6} The result of these effects is to lower serum calcium concentration. Although the physiologic role of calcitonin in bone mineral homeostasis is not yet fully understood, several investigators ^{6,7} have suggested that calcitonin acts to protect the skeleton by conserving ingested calcium.

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Our patient had undetectable basal and stimulated serum calcitonin concentrations. He seemed to improve clinically while receiving calcitonin and calcium therapies, but a bone biopsy showed that the clinical improvement was due to an increase in bone formation rather than a decrease in bone resorption.

Calcitonin therapy may have failed to decrease bone resorption in our patient for four reasons: (1) The dose may have been too low.8 (2) In vitro bone will lose its calcitonin receptors with long-term exposure to calcitonin.6 (3) Calcitonin may lower serum calcium concentration and induce secondary hyperparathyroidism.9 Our patient had normal serum calcium and PTH concentrations and tubular reabsorption of phosphorus throughout his course, yet his last bone biopsy showed qualitative evidence of hyperparathyroidism. (4) Calcitonin deficiency may not have caused the osteoporosis. The role of calcitonin in IJO is not known. A review of the literature identified one girl with IJO who had a normal basal calcitonin concentration10 and another girl with IJO who responded to empiric calcitonin therapy.11 Stevenson et al12 described a 19-year-old man with severe idiopathic osteoporosis and calcitonin deficiency whose

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In addition to calcitonin deficiency, high serum concentrations of calcitriol were noted at diagnosis, between calcitonin trials, and at the end of the 40-month observation. Parathyroid hormone stimulates and calcitonin may inhibit calcitriol production in animals. Serum concentrations of calcitonin and calcitriol seemed to vary inversely in our patient.

Hormonal changes at puberty may have stimulated calcitonin production. Estrogens increase calcitonin levels in women,⁶ and hypogonadic men with osteoporosis have lower calcitonin levels.¹⁴

As assays of bone mineral metabolism become more widely available, other subtle defects in patients with IJO may be detected.³ Despite the association of calcitonin deficiency with excessive bone resorption in this child, a therapeutic role of exogenous calcitonin was not demonstrated.

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In Other AMA Journals

JAMA

Pyrogenic Reactions Associated With the Reuse of Disposable Hollow-Fiber Hemodialyzers

S. M. Gordon; M. Tipple; A. Bland; W. R. Jarvis (JAMA 1988;260:2077)

Prevention of Accidental Extubation in Newborns

Mark S. Brown, MD

 Maintaining endotracheal intubation is critical to treating respiratory failure in newborns. To reduce accidental extubations in our neonatal intensive care unit, a prospective comparison of rates of extubation was made between two taping methods and whether or not a head restraint was used. One tape method was significantly better at preventing accidental extubations. Head restraint was not a benefit when used prospectively. Factors that preceded or were associated with accidental extubation included the time intubated, infant agitation, endotracheal tube suctioning, the infant turning its head, chest physiotherapy, loose tape, too short a tube between lip and adapter, weighing, and endotracheal tube taping. This information and the study design are valuable in developing strategies to minimize accidental endotracheal extubation and the subsequent risks of airway injury and subglottic stenosis in sick newborns.

(AJDC 1988;142:1240-1243)

Successful management of respiratory failure in newborns is the cornerstone of newborn intensive care. Endotracheal intubation is an integral part of this respiratory therapy, and accidental extubation in a sick newborn with respiratory failure can cause rapid deterioration and, often, a difficult recovery. Frequent reintubations may result in airway trauma and subglottic stenosis.14 To reduce accidental extubation, recommendations have been made to minimize traction on the tube and to securely anchor the endotracheal tube.5-9 A variety of methods of taping or anchoring the tube have been reported, although most have not been used on a systematic basis. 4,10-17

To decrease accidental extubations, 18 we devised a prospective study to compare rates of accidental extubation when two different taping methods were used and whether or not a head restraint was used. In addition, the occurrence of certain infant activities and nursing and respiratory care procedures before accidental extubations were recorded to determine which factors preceded or were associated with accidental extubations.

METHODS

All intubated newborns admitted to the newborn center at The Children's Hospital, Denver, from June 1, 1983, through Nov 30, 1983, were entered into the study. The study design involved prospective comparison of rates of accidental extubation between two different endotracheal tube taping methods and head restraint, all of which were currently in use.

Taping method 1 used two strips of 1-in cloth tape attached to the cheek over dried benzoin, each split in a Y up to the corner of the month (Fig 1). The inner leg of each Y was wrapped in a spiral fashion around the tube for at least two wraps, and the remaining leg was attached to the upper or lower lip. Taping method 2 used elastic tape cut in an H; one side of the Hwas applied as a mustache over dried benzoin, and the other side was wrapped in a spiral fashion around the tube for at least two complete wraps, first one leg, then the other (Fig 1). A small tab was folded back at the end of these halves to facilitate removal. A second type of tape, pink tape or Hy-Tape (Hy-Tape Surgical Products Corp, New York), was placed diagonally from the skin of the zygoma over the elastic tape on the tube, wrapped around once, and then taken back up to the skin of the other zygoma. In addition to being water resistant, the pink tape does not stretch, and the approach to the tube from a second angle improved the tube's stability. Benzoin was not routinely applied to the tube in either method.

The other patient-care practice studied was head restraint. This consisted of a rolled diaper fastened snugly across the head diagonally from one side of the bed to the other, overlying the side of the face (Fig 2). This was left in place at all times unless patient care required access to the head or endotracheal tube.

Thus, there were four groups of care practices: tape method 1 with or without head restraint and tape method 2 with or without head restraint. In addition, infants were stratified by birth weight (<1500 g or >1500 g). Care practices were assigned randomly on admission for each of the two weight groups and continued until intentional extubation, death, or 28 days of postnatal age. Oral intubation has been the standard of practice since 1978.18 Nasal tubes were not changed as part of the study; they were changed only at the attending physician's discretion. Daily rounds were made by one of six nurses to review each infant's bedside chart for medications and extubations and to inspect the infant for compliance with the assigned care practices.

A six-month study period was projected based on the number of infants who were intubated and admitted, the current estimated rate of extubation, and an ideal 50% drop in accidental extubations by successful care practice. The rate of extubation was expressed as the number of accidental extubations per 100 patient-days of intubation. At two-month intervals the data were analyzed. This study was reviewed by the institutional review board.

Patients were excluded from data analysis if they met any of the following conditions over half the time they were intubated: (1) if the incorrect study protocol was being used for either tape method or head restraint, (2) if they were nasally intubated, (3) if they were paralyzed, or (4) if they were sedated.

Statistical analysis was by χ^z to compare rates of extubation, Student's t test to compare means, and Poisson regression to

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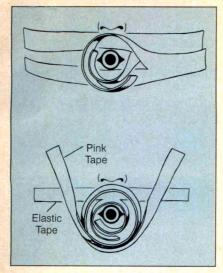


Fig 1.—Top, Taping method 1 utilized two strips of one-inch cloth tape partially split in Y and taped to side of face, with one leg of each piece taped to tube and other leg taped to upper or lower lip. Bottom, Taping method 2 used elastic tape split into H, with one side taped to middle-upper lip and other side taped to tube. Next, ½-in strip of pink tape was taped from skin over one zygoma down to tube, around, then back up to other side of face.

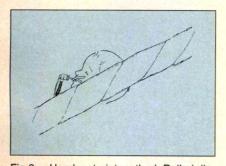


Fig 2.—Head restraint method. Rolled diaper was placed diagonally across infant's head and fastened snugly under or to mattress.

analyze factors predicting the rate of extubation.

RESULTS

During the six-month study period a total of 269 newborns were admitted to the newborn center, and 206 (77%) were intubated. Three infants were not enrolled; one died and two were extubated before randomization. One hundred forty-one infants underwent successful extubation at younger than 28 days of age, 23 died, and 39 reached

28 days of age still intubated. There was a total of 2158 patient-days of intubation (5.9 years); 805 days in infants with a birth weight greater than 1500 g (6.6 days per patient) and 1353 days in infants with a birth weight lower than 1500 g (16.7 days per patient) (Table 1).

A total of 71 patients (35%) were excluded from analysis; 35 were excluded because of lack of head restraint, ten because of the wrong tape method, 18 because of nasal intubation, five because of paralysis, and three because of sedation. There were no differences between excluded and included patients in birth weight or gestational age.

After four months, data analysis revealed that taping method 2 was significantly better. For the remaining two months, only taping method 2 was used, and infants were randomized to receive head restraint or not. After the six-month study period, there was no difference in the extubation rate between infants with head restraint and those without (Table 2).

Accidental extubations occurred a total of 94 times, for an overall extubation rate of 4.4 per 100 days of intubation. Of these, 30 (32%) were picked up from the bedside chart alone, 49 (52%) from both the bedside chart and the extubation logs, and 15 (16%) from the extubation logs only. Accidental extubations were itemized by the hour of the day and occurred evenly thoughout 24 hours. After the excluded patients were dropped there was a total of 64 extubations, for a rate of 4.2 per 100 days.

There was no difference between the two weight groups in the extubation rate expressed per 100 days of intubation (Table 1). By Poisson regression analysis the most significant factor predicting extubation, regardless of birth weight, was the time intubated (P < .0001); next was the taping method (P < .02). Therefore, because the smaller infants were intubated longer as a group, they had accidental extubations more often. Only 28 (23%) of the 122 infants with a birth weight greater than 1500 g had extubations, while 34 (42%) of the 81 infants with a birth weight less than 1500 g had extubations (P < .04). The importance

of the time of intubation is supported by the fact that the infants who had accidental extubations in both weight groups had been intubated significantly longer compared with those who did not have extubations (Table 1).

Although nasal intubation was not part of this study, only one accidental extubation occurred in these 18 infants during a total of 93 days of intubation, for an extubation rate of 1.1 per 100 days. This extubation rate was consistent with other reports in the literature of better endotracheal tube stability with nasal tubes. 18,19

Activities around the time of accidental extubation were tabulated from the extubation logs. These logs were completed for 64 (68%) of the 94 recorded extubations, with a total of 93 responses (Table 3). Agitation and suctioning of the endotracheal tube were the most frequent preextubation activities reported. These were followed by nothing being noticed, the infant turning its head, and the infant receiving chest physiotherapy. Despite the improved skin adherence of the elastoplast and pink tape, skin abrasion was not more of a problem in the infants on whom these tapes were used.

COMMENT

The use of an uncuffed endotracheal tube in newborns makes meticulous attention to securely anchoring the endotracheal tube to the face or head imperative to prevent accidental extubation. Accidental extubations in newborns can be reduced by evaluation of the taping method and by increased awareness of the risk factors associated with accidental extubation. These factors include the time intubated, agitation, endotracheal tube suctioning, head turning, chest physiotherapy, loose tape, too short a tube between lip and adapter, weighing, and endotracheal tube retaping.

The important elements of any successful tube-anchoring method include resistance to oral secretions while maximizing the stability of the tube against inadvertent traction from head movement, suctioning, or respirator tubing. ^{5,7,9} Adhesive tape, which is readily available and easy to apply,

| Table 1.—Pat | ient Characteristi | cs* | |
|--|--------------------|-------------|--------|
| | Birth W | eight, g | |
| Characteristic | <1500 | >1500 | P† |
| No. of patients | 81 | 122 | |
| Birth weight, g | 1024 (285) | 2420 (610) | |
| Gestational age, wk | 28.1 (3.5) | 35.7 (3.2) | |
| No. [%] of patients with extubations | 34/81 [42] | 28/122 [23] | <.04 |
| Time intubated, d Total | 16.7 (6.5) | 6.6 (5.9) | <.0001 |
| Extubations | 24.0 (7.2)‡ | 13.8 (9.2)‡ | <.0001 |
| No extubations | 12.6 (6.1)‡ | 4.4 (4.9)‡ | <.0001 |
| Rate of extubation, No./100 patient-days | 4.3 | 4.5 | NS |
| Postnatal age at extubation, d | 14.9 (2.1) | 9.5 (3.2) | <.0001 |
| No. of extubations, No. [%] of patients | 20 [59] | 24 [86] | |
| 2 | 9 [26] | 1 [3.5] | |
| 3 | 3 [9] | 2 [7] | |
| 4 | 1 [3] | 0 | |
| 5 | 0 | 1 [3.5] | |
| 6 | 1 [3] | 0 | |

^{*}Values are mean (SD) where parentheses are used.

[‡]P<.0001 for extubations vs no extubations within birth-weight group.

| Study Group | No. of Patients | Time Intubated, d | No. of Extubations | Rate of Extubation, No./100 Patient-Days |
|---------------------------------------|--------------------|----------------------|--------------------|--|
| Taping method 1, no head restraint | 36 | 356 | 24 | 6.7* |
| Taping method 1, head restraint | 22 | 281 | 18 | 6.4† |
| Taping method 2, no head restraint | 53 | 589 | 15 | 2.5* |
| Taping method 2, head restraint | 31 | 266 | 7 | 2.6† |
| Total | 142 | 1492 | 64 | 4.2 |

^{*}P<.001 for taping method 1 vs 2 with no head restraint.

[†]P<.03 for taping method 1 vs 2 with head restraint.

| Activity | No. (%) of Patients |
|---|---------------------|
| Infant was agitated | 14 (15.5) |
| Endotracheal tube suctioning | 12 (13) |
| Nothing specific noted | 11 (12) |
| Infant was turning its head | 10 (11) |
| Infant was receiving chest physiotherapy | 10 (11) |
| Tape was too loose | 8 (8.5) |
| Endotracheal tube from lip to adapter was too short | 6 (6.5) |
| Head restraint was off | 5 (5.5) |
| Infant was being weighed | 5 (5.5) |
| Endotracheal tube taping | 4 (4) |
| Endotracheal tube was too high | 3 (3) |
| Infant was being fed | 2 (2) |
| Infant was being turned over | 1 (1) |
| Blood samples were being taken | 1 (1) |
| Hand ventilation | 1 (1) |

is most often used; however, tape is likely to lose adhesiveness from constant exposure to oral secretions. Thus, with any movement of the head, endotracheal tube, or respirator tubing, loss of adhesiveness can result in accidental extubation. To circumvent this problem, a variety of approaches have been reported or recommended, including the following: waterproof tape8,20; sutures or pins through the tube 5-7,15,21; tape from the tube around the neck6,10; rigid devices, such as an umbilical clamp, 11,12 nasal airway, 13 Logan bow,4 cable or suture ties,15,16 or Rottenrow holder17; and a lever arm support of the respirator tubing.14 Nasal tubes also provide the advantages of avoidance of oral secretions and increased stability, and they are associated with decreased accidental extubations and subglottic stenosis. 18,19 However, nasal intubation is not commonly used because of the greater skill required, trauma to the nose and nasal septum, and concern for trauma to the eustachian tubes and infection. 7,10,21-23 The success of any of these approaches lies in improving tape adhesiveness or avoiding tape or oral secretions altogether and in decreasing traction on the endotracheal tube or minimizing head movement away from the endotracheal tube. The current study documents the importance of tape adhesiveness in reducing accidental extubation and emphasizes specific factors in infant activity and care that may increase traction on the tube, resulting in accidental extubation.

Evaluation of the impact of head restraint in this study was difficult because of the large number of patients dropped from the head restraint groups. The restraint was often inadvertently left off after care was administered to the infant, and better compliance would have been necessary to have adequately evaluated the benefit of routine head restraint. When the extubation logs were reviewed, one third of the accidental extubations recorded were associated with movement of the infant's head away from the endotracheal tube; for example, when the infant turned its head or was agitated. Head restraint may benefit infants who are stronger or more eas-

tNS indicates not significant.

ily agitated, such as large infants or infants who have been intubated a long time.

The extubation logs were a valuable source of information and served to punctuate the importance of any accidental extubation. Factors associated with accidental extubation that were found from these logs can be divided into inadequate tube stability and events that put additional traction on the tube. These two categories could be additive; loose tape might result in accidental extubation when additional traction is put on the tube. Awareness of these factors in caring for an intubated newborn, using a second or third person to assist during the procedures, and replacing loose tape would minimize accidental extubations during necessary care.

As might be expected, the time of intubation was the most significant risk factor identified for accidental extubation. As a result, a larger pro-

portion of the smaller infants had extubations. It is important to pay attention to endotracheal stability when designing care strategies for infants who are likely to remain intubated for a long time.

Several important patient-care issues can be addressed to minimize accidental extubations in sick newborns, similar to those reported in older infants24: (1) We can reduce the impact oral secretions have on loosening the tape on both the endotracheal tube and face. This may include a different tape, suture or pin through the tube, a rigid device, or moving the tape as far as possible from the mouth while still providing maximum stability. (2) Care of the endotracheal tube and tubing during suctioning, weighing, feeding, or turning the infant may require an assistant to hold the tube to ensure its stability and decrease tube traction. (3) For infants who are easily agitated while intubated, especially those intubated for a long time, minimizing agitation and head movement away from the tube may be important. This information is important in increasing awareness of risk factors for accidental extubation and, thus, preventing recurrent extubations and complications of frequent reintubations. The approach used in this study is an important tool in critically evaluating not only other methods of preventing accidental extubation but also other patient-care activities.

I appreciate the cooperation and support of the medical, nursing, and respiratory therapy staff of the newborn center at The Children's Hospital, especially the diligent efforts of the six intensive care nursery nurses who made this study possible by making daily bedside chart rounds and who continued to display enthusiasm throughout the study: Kathy Mennick, BSN, Sheryl Miller, BSN, Mary Jo Glugla, MSN, Maryann Ruiz, BSN, Julie Gosen, MSN, and Evelyn Swanton, BSN. I thank Dennis Luckey, PhD, for statistical analysis assistance, Jhonna Mc Henry for manuscript paration, and David Chavez for figure preparation.

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In Other AMA Journals

JAMA

Adverse Effects and Pyrogenic Reactions During Hemodialysis V. E. Pollak (JAMA 1988;260:2106)

Propranolol Treatment for Childhood Posttraumatic Stress Disorder, Acute Type

A Pilot Study

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• We report 11 cases of posttraumatic stress disorder. Each child had been physically abused or sexually abused or both and presented in an agitated, hyperaroused state. Using a B-A-B (off-onoff) medication design in a clinical setting, the children were treated with the beta-adrenergic antagonist propranolol. Scores on an inventory of symptoms of posttraumatic stress disorder indicated that patients exhibited significantly fewer symptoms while receiving medication than either before or after they received medication.

(AJDC 1988;142:1244-1247)

Posttraumatic disorder stress (PTSD) is defined in DSM-III1 as follows: (1) the existence of a recognizable stressor that would evoke significant symptoms of distress in almost everyone; (2) reexperiencing the trauma, as evidenced by recurrent and intrusive recollections of the event, recurrent dreams of the event, or suddenly acting or feeling as if the traumatic event were recurring; (3) numbing of responsiveness to or reduced involvement with the external world. as shown by constricted affect, feelings of detachment or estrangement from others, or markedly diminished interest in significant activities; and (4) at least two of the following symptoms that were not present before the trauma: (a) hyperalertness or exaggerated startle response, (b) sleep disturbance, (c) guilt about surviving when others did not, (d) memory impairment or trouble concentrating, (e) avoidance of activities that arouse recollection of the trauma, and (f) intensification of symptoms on exposure to events that symbolize or resemble the traumatic event.

Propranolol hydrochloride is a beta-adrenergic blocking agent that has treatment applications in a variety of medical specialties, including cardiology,^{2,3} neurology,^{4,5} and hepatology,⁶ In psychiatry, this agent has been used for the treatment of anxiety disorders,^{7,8} acute panic attacks,⁹ rage outbursts and aggression in braindamaged adults,^{10,11} schizophrenia unresponsive to neuroleptics alone,^{12,18} and side effects of neuroleptic medication.¹⁴

Recent reports have described the use of propranolol to treat adults with temper outbursts and residual attention deficit disorder (ADD). Recently the treatment of temper outbursts in 13 adult subjects yielded an unexpected and "rather dramatic" improvement in residual symptoms of ADD in 11 patients, suggesting a need for additional controlled studies. 15 In another study a sample of children and adolescents presented with organic brain dysfunction, with uncontrolled rage outbursts that were not responsive to medication and psychotherapy. 16 The investigators indicated that three fourths of their 30-patient sample demonstrated moderate or marked improvement in control of rage outbursts and aggressive behaviors. They speculated that the positive effects of propranolol were due at least in part to a beta-adrenergic blockade that modified interactions on a physiologic level among stress, anxiety, and physical sensation. On the basis of these results, further systematic research with propranolol was recommended. A controlled study¹⁷ of propranolol treatment for childhood migraine revealed neither clinical improvement nor increased adverse effects compared with placebo.

There is increasing evidence that symptoms of PTSD reflect a complex and persisting psychophysiologic conditioning created by traumatic exposure and sustained by heightened aureactivity. 18-21 tonomic Typically, autonomic arousal is heightened by exposure to stimuli that resemble or symbolize the traumatic events. These considerations have led to some experimental use of propranolol for the treatment of PTSD in patients with combat-related symptoms. Symptom improvement was observed in 11 of 12 subjects with combat-related PTSD treated with propranolol.22 The positive impact on symptoms included reports of lessened explosiveness, fewer nightmares, less intrusive thoughts of combat, lessened startle response, lessened hyperalertness, and improved sleep. Eleven subjects also reported positive changes in self-assessment at the end of the medication trial, and eight reported evidence suggesting improvement in psychosocial adaptation. More systematic research with propranolol was recommended.

Reports that propranolol has a positive effect on combat-related PTSD, affective and rage outbursts, and residual ADD in adulthood indicate the need for well-controlled clinical trials in adult populations. The cases reported below suggest that propranolol may have application in some similar child psychiatric populations and that well-controlled trials with propranolol are warranted with some groups of child patients.

PATIENTS AND METHODS

There were four boys and seven girls in the study. The mean age of the participating children was 8½ years.

In each of the 11 children included in this study, PTSD, acute type, was diagnosed by *DSM-III* criteria. The children initially presented to one of three sites: (1) an outpatient psychiatry clinic in a general

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pediatric hospital, (2) an inpatient residential facility, and (3) a juvenile court clinic for child evaluation in child custody cases in which severe child abuse is alleged. Following the initial diagnosis of PTSD by the primary clinician, one of us (R.F.) confirmed the diagnosis by a single 90- to 120-minute clinical interview.

After confirmation of DSM-III-diagnosed PTSD, acute type (onset of symptoms within six months of the trauma and duration of symptoms less than six months), the authors completed an inventory of childhood PTSD symptoms. This is a 33-item inventory on a scale of 0 to 3 that includes all the DSM-III criteria of PTSD. Each child was also initially rated on the Reaction Index,28 which has been used in childhood PTSD. Ratings on the Reaction Index describe the child's symptoms as none, mild, moderate, severe, and very severe; they are included in Table 1 along with the PTSD inventory scores. The PTSD inventory was subsequently modified by adding 13 questions to the unchanged DSM-III criteria to more effectively reflect the characteristics of childhood PTSD. This inventory is listed in Table 2 and has been previously used as a measure of the differences between the acute and chronic forms of PTSD. It appears to be a valid measure of PTSD and seems to be useful in defining different subgroups of childhood PTSD (R.F., R.K., T.F., unpublished results, June 1988).

A total score using the PTSD inventory was obtained at the time of presentation. Each of the 33 items was assigned a number between 0 and 3 depending on the intensity of the symptom; 0 indicates not at all; 1, rarely; 2, sometimes; and 3, often. The total score for each child was obtained by simply adding the numbers for each of the 33 items, yielding a possible total between 0 and 99.

Full informed consent was obtained from a parent or guardian for a four-week trial of the beta-blocker propranolol. Before treatment was begun, each child underwent a physical examination, electrocardiogram, blood pressure and pulse determination, liver function tests, and a complete blood cell count and differential determination. No child was included if there was a history of mental retardation, schizophrenia, major depression, asthma, bradycardia, hypotension, hyperthyroidism, or pervasive developmental disorder.

Propranolol hydrochloride was administered three times per day, and the starting dosage was 0.8 mg/kg/d. The dosage was gradually increased over a two-week period until a top dosage of approximately 2.5 mg/kg/d was reached. The dosage was increased unless the diastolic blood pressure fell below 55 mm Hg or the pulse rate

Table 1.—Reaction Index Ratings and Childhood PTSD* Inventory Scores

| | Initial Booting | | Childhood PTSD Inventory Score | |
|------------------------|-----------------------------|---------------------|-----------------------------------|--------------------|
| Patient No./Age, y/Sex | Reaction Index Rating | Before Treatment | During Treatment | After Treatment |
| 1/12/M | Severe | 37 | 20 | 31 |
| 2/6/F | Very severe | 42 | 21 | 38 |
| 3/10/F | Very severe | 49 | 18 | 45 |
| 4/7/F | Moderate | 30 | 28 | 26 |
| 5/10/F | Moderate | 35 | 14 | 29 |
| 6/11/M | Severe | 46 | 30 | 41 |
| 7/8/F | Very severe | 48 | 36 | 50 |
| 8/7/F | Moderate | 31 | 32 | 35 |
| 9/8/F | Severe | 51 | 23 | 44 |
| 10/8/M | Severe | 37 | 40 | 41 |
| 11/6/M | Moderate | 25 | 25 | 18 |
| Mean | | 39 | 26 | 36 |

^{*}PTSD indicates posttraumatic stress disorder.

decreased to 55 beats per minute or less. The blood pressure and pulse rate were determined twice weekly, and these measures were always obtained before the total daily dosage was increased.

From the start of treatment the patient's parent or guardian understood that the medication would be given for four weeks and then tapered over a fifth week. It was also understood that the child would be closely followed up with a repeated cardiogram and blood pressure and pulse rate determinations. Also, a clinical interview and the childhood PTSD inventory were to be completed during treatment (day 21 to 28) and three weeks after the medicine was fully discontinued.

The authors were not the primary therapists for the children, who all received individual treatment during this entire period. Three children were hospitalized, two were receiving residential treatment, and four others received family treatment on an outpatient basis. No other psychotropic medications were employed during the treatment period.

According to the initial agreement, children judged to have a positive response were offered continued treatment (after the study period), while those who did not respond favorably or could not tolerate the medicine did not receive it after discontinuation.

PATIENT REPORTS

PATIENT 1.—A boy 12 years 1 month old was admitted to the hospital due to aggressive behavior, agitation, somatic complaints, and reported "loss of control." Symptoms that began approximately five months before admission and that generally had been increasing in intensity included the following: abdominal pain, loss

of interest in sports, irritability, exaggerated startle response, initial insomnia, nightmares of sexual abuse, sense of pessimism, heightened impulsivity, avoiding male family members, and decreased school performance. Parents and school personnel were unable to provide adequate structure as the child became oppositional and angry.

Medical and developmental history revealed a normal pregnancy, delivery, and birth, and milestones were reached at appropriate ages. There was some impulsivity but no affective disorder, conduct disorder, or psychosis. Results of medical review of systems were unremarkable. Results of physical examination were within normal limits, as were an electroencephalogram and an electrocardiogram. School records revealed that the patient was about one year behind in reading and spelling. The Wechsler Intelligence Scale for Childrenrevised revealed a full-scale IQ score of 96.

The family constellation included the mother and father and three siblings aged 7, 15, and 17 years. About two years before the patient was admitted, allegations of sexual abuse were filed with a state social service agency, but the results of the investigation were inconclusive. The family psychiatric history was positive only for the mother's major depression. Treatment was recommended, but the family was not compliant.

The child spoke rather directly about the sexual abuse he had experienced. He related well to the interviewer. He accused his father of recent sexual abuse as well as physical abuse of long-standing duration. The child was agitated, distractable, physically active, anxious, and unable to attend to tasks appropriate to his age. He was impulsive, angry, and frightened of his father. His affect seemed sad but there was

| | | PI | D Score | |
|--|---|--|--|---|
| | 0 | 1 (Parabi) | 2 (Sometimes) | 3 (Often) |
| ltem - | (None) | (Rarely) | (Sometimes) | (Oiteii) |
| Recurrent and intrusive recollections | *************************************** | | |) . |
| Fraumatic play (recreates trauma themes) | | | Special property and the second | *************************************** |
| Nightmares, distressing dreams | *************************************** | | | |
| Acts as if traumatic event were occurring | | ~~~~ | | |
| Distressed at exposure to symbolic events | | **** | description of the same | |
| Avoids thoughts and feelings related to trauma | | ***** | | |
| Avoids activities that arouse recollections | | <u></u> | *************************************** | |
| nability to recall aspects of trauma | *************************************** | | | ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, |
| Diminished interest in activities or games | *************************************** | | 4,000,000,000 | |
| oss of developmental skills, regression | | | | |
| Detachment or estrangement from others | | 49444 | | |
| Restricted range of affect | | | | |
| Thinks or says life will be short | | *************************************** | | *************************************** |
| Difficulty falling asleep | washing. | | 444,444,444 | |
| Difficulty staying asleep | - | | | |
| Irritable, angry | | *************************************** | 36-400-Anto-Control Anto- | |
| Aggressive outbursts | | *************************************** | *************************************** | |
| Difficulty concentrating | | | ************ | *********** |
| Hypervigilant | | | | |
| Exaggerated startle response | *************************************** | | | *************************************** |
| Physiologic reaction to symbolic exposure | | | | |
| Generalized agitation, anxiety | | *************************************** | *********** | |
| Distortion of reality testing | | *************************************** | Colonia Control Colonia Coloni | |
| Sexually provocative or inappropriate behavior | | | gain and publication of the contraction of the cont | in in the interior |
| Odd behavior or statements | | | | , |
| lmaginary companions | | | - Approximation of the second | |
| Physical complaints of vague origin | | | | |
| Excessive daydreaming | ************ | announted to the state of the s | | |
| Illusions, vivid images | | *************************************** | annual trade de de Compte. | |
| Thinks life will be difficult, hard | | ************** | and the second s | ************ |
| Sad, unhappy | | | | |

^{*}PTSD indicates posttraumatic stress disorder.

Sense of emptiness

no excessive guilt or self-depreciation. The range of affect was full and appropriate but he was excitable. His language skills seemed mildly below his age level but the content of his speech was within normal limits. There was no evidence of suicidal ideation or plans, and there was no disturbance of reality testing. There was no disturbance of memory or orientation.

The child reported difficulty falling asleep, without midinsomnia. On occasion he had nightmares of sexual assault and physical injury. He said he thought his future life would be difficult, and he be-

lieved he would experience more sad than happy events. He did not know what he would do when he grew up and did not offer any wishes when asked. While he engaged in some play, he did not play for any length of time, and the themes tended to be aggressive. He admitted to feeling mad and angry at times but did not know why.

The child spoke about his desire not to return home, although he wished to see his siblings. He expressed concern for the safety of his siblings. He denied any illusions or hallucinations.

He had an initial score of 37 on the

childhood PTSD inventory at the time of his hospital admission. After informed consent was obtained, propranolol hydrochloride treatment was begun at 0.75 mg/kg/din three divided doses. The dosage was increased to 2.2 mg/kg/d by two weeks. Three weeks into the treatment his score was 20, and approximately one month after treatment was discontinued his score was 31. He was discharged and placed in a foster home after a three-month stay. Propranolol treatment was restarted before discharge, and he continued to receive the medication as an outpatient until the majority of his symptoms subsided. No significant adverse effects were noted.

PATIENT 2.—A 6-year-old girl presented to her pediatrician with abdominal pain and vaginal irritation. Results of physical examination were consistent with sexual abuse. Recent new symptoms included somatic complaints, initial insomnia, panic states, exaggerated startle response, agitation, fearfulness, and frequent worrying.

The pregnancy, birth, and neonatal periods were unremarkable. There was no history of anxiety, aggression, depression, or somatic complaints before the onset of abuse. The medical history was unremarkable, and results of the physical examination were negative except for the vaginal irritation.

Her full-scale IQ score was 109, and her school achievement and performance were appropriate for her age, although her school performance had declined in the months before admission.

The family consisted of the mother, a 14-year-old brother, the patient, and, periodically, the mother's boyfriend. The biologic father never was involved with the family and lived out of state. The mother was an active alcoholic, and the family psychiatric history was positive for probable antisocial personality disorder (father) and learning disability (brother).

The patient's mental status was remarkable for agitation, hypervigilance, tenseness, and some dysphoria. Although she did not identify anybody by name, using doll play, she described sexual acts perpetrated by an older man against a female child. There was no evidence of any major affective or thought disorder, and her affect, while agitated, was appropriate. The form and content of her language were normal for a child of her age, and she related well to the interviewer. She described her fear of men and her general discomfort when she was with men, but this did not apply to boys of her own age. She admitted that she felt unhappy and worried that her life might be difficult. On one or two occasions she had a transient vision of her mother's former boyfriend, but otherwise there were no delusional or

hallucinatory phenomena inappropriate for her age. Notably, just touching the child on the shoulder resulted in an extreme reaction, and she would scream "Don't hurt me."

The child had previously been treated with both individual and family therapy. The mother had entered therapy for her alcohol abuse, resulting in a reported decrease in her alcohol intake. After two months of individual and family treatment, the patient's level of dysfunction was unchanged. At this time her score on the PTSD inventory was 42. An electrocardiogram was done, informed consent was obtained, and propranolol hydrochloride treatment was begun at 0.6 mg/kg/d in three divided doses. The dosage was increased weekly; the final dosage was 1.6 mg/kg/d. On two occasions the diastolic blood pressure was as low as 50 mm Hg, but there were no other clinical symptoms. Her improvement was significant, as documented by improved sleep, less fighting, decreased agitation, fewer manifestations of hyperarousal, and better academic performance. After 26 days her score was 21, but after treatment was discontinued her score reached 38.

The perpetrator(s) was never identified despite an extensive inquiry by a social service agency.

RESULTS

The data were analyzed by analysis of variance, with medication conditions (off-on-off) as a repeated measure. Table 1 shows that the scores on the PTSD symptom inventory were 39 before medication, 26 during medication, and 36 after treatment was terminated. The mean scores differed significantly across the three time periods (F=11.54; df=2,22; P<.0005). Post hoc tests revealed a significant improvement during treatment compared with before medication (F=13.05; df=1,10; P=.0048) and a significant decrement after treatment compared with during medication (F=10.52; df=1,10; P=.0088).

Several adverse effects were noted during the medication period. While no child experienced hypotension or bradycardia, the dosage prescribed in two children was limited due to mildly lowered blood pressure and pulse rate (compared with baseline values). One child complained of sedation, and the dosage for this child was also limited. Therefore, while no child required discontinuation of medicine, the top dosage was limited by mild adverse effects in three children.

COMMENT

The results presented above indicate that propranolol may be an effective treatment for PTSD, acute type. The fact that subjects improved while receiving medication and became worse when treatment was terminated suggests that their improvement was due to the medication rather than the passage of time or placebo effects associated with interactions with mental health personnel. However, improvement may have been caused by a placebo effect associated with the belief that the medication would be helpful rather than by an actual pharmacologic effect. Given the impressiveness of the findings, it is very likely that a placebo effect is responsible for at least some of the noted improvement. Since the treatment was offered in a clinical setting, a doubleblind, placebo-controlled study would not be appropriate. We are currently using such a design in another study of beta-blockers for the treatment of PTSD, acute type.

The clinical response of PTSD, acute type, to the administration of propranolol is not conclusive proof of involvement of the critical adrenergic system. The effectiveness of propranolol may be due to other broad pharmacologic effects that are sometimes seen with the use of beta-blockers. However, these case reports indicate that further research is warranted.

The treatment of choice in PTSD is not pharmacologic. Providing a safe environment, either an inpatient environment or an outpatient environment such as a foster home, is the initial treatment step. Pharmacologic treatment may offer significant improvement in the hypervigilant, high-arousal presentation stages of the disorder. Amelioration of the psychophysiologic symptoms may make individuals more amenable to environmental and psychotherapeutic interventions.

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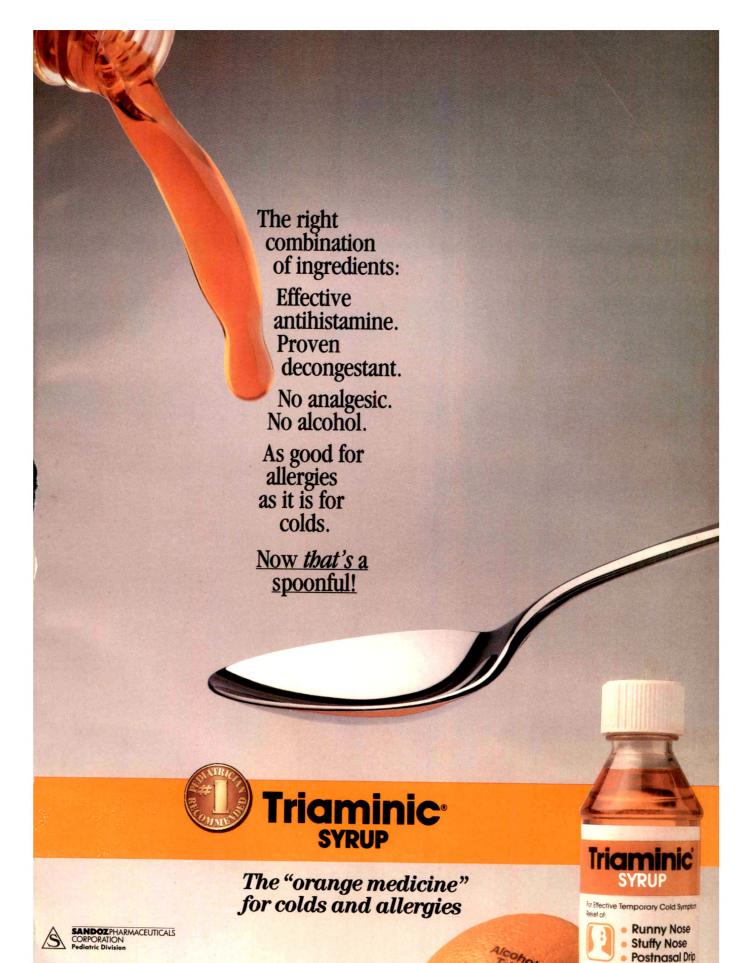
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